NOT FOR PUBLICATION

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

INSITE VISION INCORPORATED, et al., Plaintiffs, v. SANDOZ INC., et al., Defendants.	CIVIL ACTION NO. 11-3080 (MLC) **MEMORANDUM OPINION**

COOPER, **District Judge**

This action requires the Court to determine the validity of the plaintiffs' patents, i.e., U.S. Patent No. 6,861,411 ("the '411 Patent"), and the so-called "ISV Patents," i.e., U.S. Patent No. 6,239,113 ("the '113 Patent"), No. 6,569,443 ("the '443 Patent"), and No. 7,056,893 ("the '893 Patent").[1] Following an eight-day bench trial, and for the reasons that follow, the Court has determined that the claims asserted from the patents-in-suit are valid.

I. INTRODUCTION

A. The '411 Patent

The plaintiff Pfizer Inc. ("Pfizer") owns the '411 Patent, which is entitled "Method of Treating Eye Infections with Azithromycin." (U.S. Patent No. 6,861,411, at [54], [73] (filed

[1] The '893 Patent's full number is "7,056,893," not "7,059,893" as incorrectly referenced by the plaintiffs in some of their submissions. (See, e.g., dkt. entry no. 110, Pls.' Trial Br. at 1 n.1; dkt. entry no. 171, Pls.' Post-Trial Br. at 1 n.1 (hereinafter "Pls.' Post-Trial Br.").)

Nov. 25, 1998) (hereinafter "DTX 1").) The '411 Patent is directed to a method of treating an ocular infection by topically applying azithromycin, an azalide antibiotic, to an eye.

Pfizer has granted the plaintiff InSite Vision Incorporated ("InSite") an exclusive license under the '411 Patent. InSite, in turn, has granted the plaintiff Inspire Pharmaceuticals, Inc. ("Inspire") an exclusive sublicense under the '411 Patent.

B. The ISV Patents

InSite owns the '113 Patent, which is entitled "Topical Treatment or Prevention of Ocular Infections." (U.S. Patent No. 6,239,113, at [54], [73] (filed Jul. 2, 1999) (hereinafter "DTX 2").) The '113 Patent is directed to a process for treating an eye by topically applying a composition comprising an azalide antibiotic.

InSite also owns the '443 Patent and the '893 Patent, which both relate to the '113 Patent and have the same title as the '113 Patent. (U.S. Patent No. 6,569,443, at [54], [63], [73] (filed Jan 24, 2001) (hereinafter "DTX 3"); U.S. Patent No. 7,056,893, at [54], [63], [73] (filed June 4, 2002) (hereinafter "DTX 4").)[2] The '443 Patent is directed both to topical ophthalmic compositions comprising an azalide antibiotic and to processes for treating an eye by topically applying an azalide antibiotic. The '893 Patent is directed to compositions comprising an azalide antibiotic, methods of preparing such compositions, and methods of treating bacterial ocular infections by administering such compositions.

[2] The '113 Patent issued from U.S. Patent Application No. 09/346,923 ("the '113 Application"). (DTX 2 at [21].) The '443 Patent issued from U.S. Patent Application No. 09/767,943, which is a continuation of the '113 Application. (DTX 3 at [63].) The '893 Patent issued from U.S. Patent Application No. 10/160,060, which is a continuation-in-part of the '113 Application. (DTX 4 at [63].)

InSite has granted Inspire an exclusive license under the '113 Patent, the '443 Patent, and the '893 Patent.

C. The New Drug Application for AzaSite®

Inspire holds a New Drug Application ("NDA") that has been approved by the United States Food and Drug Administration ("FDA"), NDA No. 50-810, which describes a 1% azithromycin solution sold under the trade name AzaSite®. AzaSite® is indicated for the treatment of bacterial conjunctivitis. The FDA publication Approved Drug Products with Therapeutic Equivalence Evaluations, which is commonly known as "the Orange Book," lists, among others, the '411 Patent, the '113 Patent, the '443 Patent, and the '893 Patent in connection with AzaSite®.

D. The Abbreviated New Drug Application

The defendant Sandoz Inc. ("Sandoz") filed Abbreviated New Drug Application ("ANDA") No. 202308 with the FDA on March 3, 2011, seeking approval to manufacture, market, and sell a generic version of the 1% azithromycin solution described in NDA No. 50-810. On April 15, 2011, Sandoz sent each of the plaintiffs a notification letter, informing them that the ANDA contained a Paragraph IV certification for both the '411 Patent and the ISV Patents.[3] In that Paragraph IV certification, Sandoz contends that the claims set forth in the '411 Patent and the ISV Patents are invalid, and that, otherwise, the ANDA product will not infringe those claims.

[3] See 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

E. This Action

Pfizer, InSite, and Inspire (collectively "Plaintiffs") commenced this patent infringement action against Sandoz and related entities on May 26, 2011, pursuant to 35 U.S.C. § 271. (See dkt. entry no. 1, Compl.)[4] They allege that the ANDA product will infringe claims 3 and 5 of the '411 Patent, claims 6-9 of the '113 Patent, claims 16 and 44 of the '443 Patent, and claims 4, 6, 7, 9-12, 30, 36, and 40 of the '893 Patent (collectively, "the Asserted Claims"). (See dkt. entry no. 121, 5-23-13 Final Pretrial Order at 26.) Sandoz has responded with affirmative defenses and counterclaims, arguing that each of the Asserted Claims are invalid as obvious under 35 U.S.C. § 103(a).[5]

The Court heard the parties' claim construction arguments on June 27, 2012, and entered claim construction orders soon thereafter. (See dkt. entry no. 64, 6-27-12 Markman Hr'g Tr.; dkt. entry no. 70, 8-8-12 Claim Constr. Order; dkt. entry no. 71, 8-8-12 Stip. Claim Terms Order.) On July 20, 2012, the parties stipulated that

> [t]he manufacture, use, offer for sale or sale of Sandoz's ANDA product within the United States or the importation of Sandoz's ANDA product into the United States would infringe claims 3 and 5 of the '411 patent, claims 6-9 of

[4] Plaintiffs brought the action against Sandoz and the defendants Sandoz GmbH and Sandoz Industrial Products S.A. Because all of the defendants are related entities and have acted jointly in this action, the Court refers to them collectively as "Sandoz."

[5] Sandoz earlier argued that certain Asserted Claims were invalid for issues relating to inventorship, including lack of enablement and indefiniteness. (See, e.g., dkt. entry no. 109, Sandoz's Trial Br. at 28-30 (arguing that claim 3 and claim 5 of the '411 Patent and claim 44 of the '443 Patent were invalid pursuant to 35 U.S.C. § 112).) Sandoz abandoned each of those arguments either before or during trial. (See dkt. entry no. 156, Trial Tr. at 368 (noting that defendants withdrew the inventorship issue); dkt. entry no. 170, Sandoz's Post-Trial Br. (failing to raise those arguments and, thus, abandoning them).)

> the '113 patent, claims 16 and 44 of the '443 patent, and claims 4, 6, 7, 9-12, 30, 36, and 40 of the '893 patent under 35 U.S.C. § 271(a), (b), and/or (c), based on the Court's claim construction rulings and if the asserted claims of the '411, '113, '443, and '893 patents are not invalidated.

(Dkt. entry no. 68, 7-31-12 Stip. & Order at 2.)

An eight-day bench trial was conducted between June 11, 2013 and August 13, 2013, and the parties presented testimony, documentary evidence, and argument relating to the alleged obviousness of the Asserted Claims.[6] The parties have submitted post-trial briefs. (See dkt. entry no. 170 (hereinafter "Sandoz's Post-Trial Br."); Pls.' Post-Trial Br.) Having considered all of the evidence presented at trial and the parties' related arguments, the Court now makes the following findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a)(1).

[6] The consecutively paginated trial transcript is docketed at entry nos. 155, 156, 159, 160, 162, 163, and 166 (hereinafter "Trial Tr. at __ "). A portion of the trial transcript that was inadvertently omitted from docket entry no. 160 is separately paginated and docketed at entry no. 160-1 (hereinafter "Trial Addendum at __ "). The closing argument transcript (docketed at entry no. 173) is not consecutively paginated with the rest of the trial transcript (hereinafter "Closing Args. Tr. at __ ").

II. FINDINGS OF FACT AND CONCLUSIONS OF LAW

A. Applicable Legal Standards

1. The Burden of Proof

Each of the Asserted Claims is presumed valid. See 35 U.S.C. § 282;[7] Microsoft Corp. v. i4i Ltd. P'ship, 131 S.Ct. 2238, 2243, 2246 (2011); Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd., 719 F.3d 1346, 1352 (Fed.Cir. 2013). Sandoz thus bears the heavy burden of proving invalidity by clear and convincing evidence. See 35 U.S.C. § 282 ("The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity."); Microsoft Corp., 131 S.Ct. at 2246 ("[A] defendant raising an invalidity defense [bears] a heavy burden of persuasion, requiring proof of the defense by clear and convincing evidence." (citation omitted) (internal quotation marks omitted)). "Clear and convincing evidence places in the fact finder 'an abiding conviction that the truth of [the] factual contentions are highly probable.'" Procter & Gamble Co. v. Teva Pharm. USA, Inc., 566 F.3d 989, 994 (Fed.Cir. 2009) (quoting Colorado v. New Mexico, 467 U.S. 310, 316 (1984)).

"The burden of proof never shifts to the patentee to prove validity." Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1359 (Fed.Cir. 2007). But the Court, when determining whether Sandoz has met its burden of proof, must consider all of the evidence presented at trial, including the testimony and evidence offered by Plaintiffs. See id. at 1360.

[7] References to and quotes from Title 35 of the United States Code ("the Patent Code") that appear in this opinion refer to or quote from the Patent Code as it existed when the action was commenced in May of 2011.

2. Obviousness

A patent will not be issued or may be invalidated if the subject matter of the patent is obvious.

> A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

35 U.S.C. § 103 (hereinafter "Section 103"). "Obviousness is a question of law, which depends on several underlying factual inquiries." See Senju Pharm. Co. v. Apotex Inc., 717 F.Supp.2d 404, 418 (D. Del. 2010), aff'd, 485 Fed.Appx. 433 (Fed.Cir. 2012).

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406 (2007) (quoting Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966)).

"[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. at 418; see also Unigene Labs., Inc. v. Apotex, Inc., 655 F.3d 1352, 1360 (Fed.Cir. 2011). Instead, proof of obviousness requires proof that a person of ordinary skill in the art (hereinafter a "POSITA") "would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and . . . would have had a reasonable

expectation of success in doing so." Procter & Gamble, 566 F.3d at 994 (quoting Pfizer, 490 F.3d at 1361); see also Bayer Schering Pharma AG v. Barr Labs., Inc., 575 F.3d 1341, 1347 (Fed.Cir. 2009). Such a person would interpret prior art references "using common sense and appropriate perspective." Unigene Labs., 655 F.3d at 1361.

A claimed invention may be invalid under Section 103 if it would have been obvious to a POSITA to combine prior references that address each element of the claimed invention. "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." KSR, 550 U.S. at 421. But such, when offered under an "obvious-to-try" theory of obviousness, is insufficient unless the evidence indicates that a POSITA would have encountered only a "small," "finite," or "easily traversed" number of options. In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig., 676 F.3d 1063, 1072 (Fed.Cir. 2012), cert. denied, 133 S.Ct. 933 (2013). Indeed, "KSR did not create a presumption that all experimentation in fields where there is already a background of useful knowledge is 'obvious to try,' without considering the nature of the science or technology." Abbott Labs. V. Sandoz, Inc., 544 F.3d 1341, 1352 (Fed.Cir. 2008); see Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 520 F.3d 1358, 1363-64 (Fed.Cir. 2008); see also Leo Pharm. Prods., Ltd. v. Rea, No. 12-1520, 2013 WL 4054937, at *9 (Fed.Cir. Aug. 12, 2013); In re Armodafinil Patent Litig. ('722 Patent Litig.), MDL No. 10-2200, 2013 WL 1332523, at *39 (D. Del. Mar. 30, 2013). "When a field is 'unreduced by direction of the prior art,' and when prior art gives 'no indication of which parameters were

critical or no direction as to which of many possible choices is likely to be successful,' an invention is not obvious to try." Unigene Labs., 655 F.3d at 1361 (citations omitted).

B. Defining the Level of Ordinary Skill in the Art

Plaintiffs and Sandoz have each offered a definition of the level of ordinary skill in the art that applies to the analysis of both the '411 Patent and the ISV Patents. Those definitions are substantially similar. (Compare Pls.' Post-Trial Br. at 6, n.3, with Sandoz's Post-Trial Br. at 13.) According to those definitions, a POSITA would hold one or more degrees relating to chemistry or the pharmaceutical sciences, and have at least two years of work experience that relate to drug formulations.

Because Plaintiffs appear to agree that the differences in their definitions of the level of ordinary skill in the art do not affect the resolution of the action, the Court will not resolve those differences.

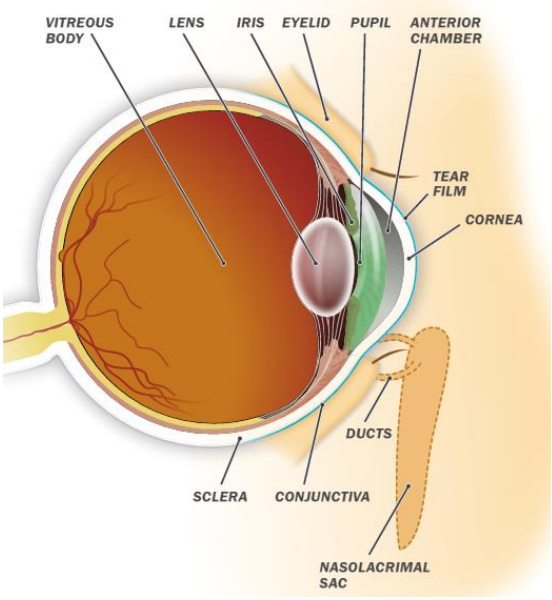
C. The '411 Patent [8]

1. The Prior Art

a. Anatomy of the Eye

As demonstrated by the image below, the eye is comprised of multiple layers, many of which act as barriers to the entry of foreign particles and substances.

[8] The '411 Patent relates to United States Provisional Patent Application No. 60/067,250, which was filed on December 2, 1997. It is thus undisputed that the '411 Patent is entitled to a priority date of December 2, 1996. (See DTX 1 at [60].) See 35 U.S.C. § 102(b); New Railhead Mfg., L.L.C. v. Vermeer Mfg. Co., 298 F.3d 1290, 1293 (Fed.Cir. 2002).



(Pls.' Ex. PTX 1024, Structures of the Human Eye (sources: Timothy S. Lesar & Richard G. Fiscella, Antimicrobial Drug Delivery to the Eye, 19 DRUG INTELLIGENCE & CLINICAL PHARMACY 642, 642 (Sept. 1985) (hereinafter "PTX 11"); Sayoko Moroi & Paul R. Lichter, Ocular Pharmacology, in THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 1619, 1620 (9th ed. 1996) (hereinafter "PTX 9")).)

i. The Tear Film

The tear film is the outermost layer of the eye, which sits on top of both the cornea and the conjunctiva. (Trial Tr. at 134.) Sandoz's expert, Dr. Matthew Goren, a practicing ophthalmologist specializing in external and corneal diseases and a faculty member of Northwestern University School of Medicine, described the tear film as "extremely thin" -- only four microns thick. (Id. at 109, 113, 134-35.) By comparison, a single red blood cell is approximately five microns thick. (Id. at 134-35.) Although it is thin, a normal, non-diseased tear film has three layers, none of which are comprised of tissue. (Id. at 135, 270, 271, 618.) The outermost layer is an oily layer -- i.e., a lipid layer -- that "is formed from glands that reside in the eyelid." (Id. at 135, 271.) The middle layer is comprised of water that is

secreted from the lacrimal or tear gland. (Id. at 135, 286, 617-18.) The innermost layer that sits over the conjunctiva and cornea is also a lipid layer. (Id. at 135, 618.) The oil comprising this innermost lipid layer is secreted from the conjunctiva's mucous membrane in order to stabilize the tear film. (Id. at 135, 147.)

Dr. Goren described the tear film as a "dynamic" structure. (Id. at 136.) Tears are constantly produced and shifted by gravity and the act of blinking. (Id.) Tears "turn over," meaning that they are generated, they move around, and they are replaced by new tears. (Id. at 286, 617.)

Substances "constantly" penetrate the tear film. (Id. at 136.) The tear film is a natural barrier, which serves to keep foreign material (including topical medicaments) out of the eye. (Id. at 285, 615-16, 957-58.) Blinking is one of the eye's protective mechanisms. (Id. at 289-90.) Noxious materials cause reflex blinking, which causes tears to wash over the eye and down the nasolacrimal duct, carrying away foreign matter. (Id. at 286, 289-90, 615-16.)

ii. The Cornea and Conjunctiva

The two outermost layers of the eyeball itself are the conjunctiva and the cornea, which, according to Dr. Goren, are "equally superficial." (Id. at 133.)

(a) The Conjunctiva

The conjunctiva is a mucous membrane that secretes mucous material to stabilize the tear film. (Id. at 135.) The inner eyelid is called the palpebral conjunctiva. (Id. at 137.) The portion of conjunctiva that covers the majority of the eyeball is known as the bulbar conjunctiva. (Id. at 133, 137-38, 620.) The conjunctiva stops where the cornea begins; there

is no overlap between the two. (Id. at 133, 137-38, 273, 619.) The conjunctiva, while permeable when healthy, is even more permeable when diseased or inflamed. (Id. at 139.)

(b) The Cornea

The cornea is contiguous with the sclera (the white part of the eye), which is covered by the bulbar conjunctiva. (Id. at 131, 151.) The cornea's function is to see and to focus. (Id. at 145.) Light enters the eye through the cornea, and, therefore, it is critical that the cornea is clear and normally shaped. (Id. at 611.) Light, which is critical to vision, must reach the retina and then the optic nerve. (Id. at 610-11.) According to Plaintiffs' expert Dr. Penny Asbell, an ophthalmologist specializing in corneal diseases and a professor of ophthalmology at the Icahn School of Medicine, "Tiny changes in that cornea, that front window, totally change quality of vision." (Id. at 596-97, 611.)

The majority of the thickness of the cornea is comprised of the stroma, which must remain clear in order to permit vision. (Id. at 275.) Foreign material or infection of the stroma can hinder eyesight. (Id. at 275.)

The outermost layer of the cornea -- the corneal epithelium -- is made of corneal epithelial cells. There is very little space between these cells. (Id. at 285-86.) According to Dr. Asbell, "hemidesmosomes" are the "tight junctions" between corneal epithelial cells that connect the cells to one another to ensure that the epithelium stays in place and that foreign particles do not penetrate the cornea. (Id. at 624-25.) These hemidesmosomes are also a barrier to the penetration of drugs through the eye. (Id. at 628-29.)

iii. Natural Ocular Barriers to Foreign Substances

The eye has five natural defenses to foreign material: (1) blinking; (2) tearing; (3) tear turnover; (4) cheek overflow drainage; and (5) nasolacrimal drainage. (Pls.' Ex. PTX 1031, Defenses of the Human Eye (source: PTX 11 at 642-43); see also Trial Tr. at 626-27.) These barriers present challenges to formulators in developing topical ophthalmic drugs and predicting whether a given topical ophthalmic drug will penetrate ocular tissue. (See Trial Tr. at 626-27, 638-39.) The development of topical ophthalmic drug delivery systems is primitive primarily due to these barriers. (OCULAR THERAPEUTICS AND DRUG DELIVERY 22 (Indra K. Reddy ed., 1996) (hereinafter "DTX 84").)

b. Ocular Infections

Many different types of bacteria can cause ocular infections. (Trial Tr. at 654; see also Pls.' Ex. PTX 1033, Many Different Kinds of Bacteria Can Cause Ocular Infection (source: DTX 84 at 229).) Each part of the eye is susceptible to infection. (Trial Tr. at 151-52, 302, 648.) An infection presenting in one part of the eye, e.g., the conjunctiva, can spread to other parts of the eye, e.g., the cornea. (Id. at 650-51.)

Among ocular infections, only conjunctival infections (i.e., conjunctivitis) and corneal infections (i.e., corneal ulcers) can be treated topically. (Id. at 152, 652-53.) To treat either, the antibiotic must reach the infected tissue and remain in contact with it for an adequate period of time. (Id. at 302-03, 652-53.)

i. Conjunctivitis and Corneal Ulcers

Conjunctivitis is a general term for inflammation of the conjunctiva. (Id. at 153.) It can be caused by, inter alia, allergens, toxicity, or a bacterial infection. (Id.)

Corneal ulcers are quite distinct from conjunctivitis. (Id. at 164.) They are most often caused by bacterial infections in the stroma. (Id. at 164-68.) The cornea's clarity is important for vision, and corneal ulcers can cause the cornea to become opaque, which may result in blindness and even loss of the eye. (Id. at 164-65.) In order for this infection to develop, there must be some sort of epithelial defect in that the epithelial cells are "missing somewhere." (Id. at 166, 168-69.) According to Dr. Goren, this absence of the corneal epithelium is beneficial to the treatment of corneal ulcers. Topical ophthalmic drugs, the preferred method for treating corneal ulcers, are better able to penetrate ocular tissue since one of the barriers to penetration is missing. (Id. at 170-71.) Topical antibiotics must still penetrate the tear film. (Id. at 171-72.)

Dr. Goren explained that it is easier to treat conjunctivitis than corneal ulcers, as a normal conjunctiva is forty to fifty times more permeable than a normal cornea. (Id. at 194-95.) The current preferred treatment for bacterial conjunctivitis is a topical, "broad-spectrum antibiotic eye drop dosed two to four times a day for anywhere between three and seven days." (Id. at 173.) There are approximately 12 topical antibiotics approved for ophthalmic use, and Dr. Goren testified that "pretty much any topical antibiotic eye drop will effectively treat bacterial conjunctivitis." (Id. at 174.)

ii. Trachoma

Sandoz offered Dr. Sheila West -- an epidemiologist in the ophthalmology department of Johns Hopkins School of Medicine -- as an expert on trachoma. (Id. at 393-95, 402.) Dr. West is not an ophthalmologist, she does not treat patients, and she has no expertise in drug formulation. (Id. at 396-97, 403.) She testified that trachoma is a chronic, systemic disease that presents in the eye in the form of conjunctivitis. (Id. at 412-13, 492-93.) It is a self-replicating bacterium that is a leading cause of preventable blindness. (Id. at 404-09; DTX 245, Hugh R. Taylor, TRACHOMA: A BLINDING SCOURGE FROM THE BRONZE AGE TO THE TWENTY-FIRST CENTURY Foreword (2008).) If left untreated, trachoma will affect both the conjunctiva and cornea, and leave the eye exposed to other forms of infection. (Trial Tr. at 413-14.)

c. Issues to Consider When Choosing an Antibiotic

Formulators must consider many factors when developing and testing antibiotics. The adverse effects of an antibiotic must be measured against the efficacy of the treatment. (Id. at 324.)

Tonicity, which is a measure of osmotic pressure, is an important parameter in topical preparations because it relates to the tolerability of the eye. (Imran Ahmed Dep. Tr. at 67-68 (hereinafter "JTX 101").) Tonicity involves the response of cells to external solutions. (See id.) If there are tonicity issues -- if osmotic pressure is not balanced -- blood cells may burst or shrink. (Id. at 68; Trial Tr. at 788-89.) Tonicity can be controlled by adding or removing salt from a formulation. (JTX 101 at 68-69.)

Toxicity is another important consideration. Essentially anything (including topical drugs) that is put from a bottle to the eye will have some ocular toxicity. (Trial Tr. at 322-24.) A change in the formulation or administration of a drug may produce toxicities that were not present with the drug's original formulation. (Id. at 322-23.) One form of toxicity interferes with the re-growth of corneal epithelial cells. (Id. at 644-45.)

The ability of the drug to penetrate the eye's natural barriers affects the efficacy of any topical drug because it determines whether the drug reaches the infected tissue to treat the infection and prevent any spread. (Id. at 652-53.) According to Dr. Asbell, a POSITA would prefer a drug that penetrates both conjunctival and corneal tissues. (Id. at 652-53, 661.)

Ophthalmologists typically treat eye infections without taking cultures that would determine which of the many known bacteria or viruses caused the infection at issue, and thus, they would prefer to use well-tolerated, broad-spectrum antibiotics. (See id. at 308-09, 658-59.) This ensures that various types of infections are treated without the need for expensive, time-consuming testing.

Other important factors in choosing an antibiotic include the cost of the antibiotic, its side effects, and patient compliance. (See id. at 486-88.) A patient's failure to complete a dosing regimen can render that dosing regimen less than fully effective and can leave behind organisms that are more resistant to the treatment. (Id. at 487-88, 668-69.)

i. Systemic (Oral) Versus Topical Treatments, Generally

According to Sandoz's expert Dr. Kenneth Reed -- a doctor of pharmaceutical sciences specializing in ophthalmics but who is not a medical doctor -- and to Dr. Goren, a

treating physician would prefer not to use an oral (or systemic) antibiotic to treat conjunctivitis. (Id. at 176-77, 514, 533-41, 555-56, 941-42.) Potential problems relating to the systemic delivery of drugs, such as side effects, resistance to organisms, and allergies, are not observed when the drug is applied topically. (Id. at 177; see also DTX 84 at 233.) With topical application, the antibiotic can be placed directly on the site of infection, thereby delivering a high concentration of the drug. (Trial Tr. at 177, 218.) Dr. Reed explained that, with lower concentrations of the antibiotic, some bacteria may not be killed off and may develop a resistance to the antibiotic; therefore, formulators prefer to attain high concentrations. (Id. at 555-56.)

Sandoz's experts Dr. Reed and Dr. Goren testified that a formulator would expect that a drug known to be successful when systemically administered would be successful when applied topically, given the assumption that higher concentrations could be achieved by topical application at the site of the infection. (Id. at 231, 908-11, 990-97.) However, Plaintiffs' expert Dr. Asbell disagreed with Dr. Goren's and Dr. Reed's conclusion that a formulator could simply take a drug that is known to work systemically and expect it to work when applied to the eye, topically. (See id. at 638-39.) For example, cyclosporin worked well when administered orally but did not work well when applied topically to the eye. (Id. at 638.) According to Dr. Asbell, a POSITA would not assume that delivering high concentrations of a drug to the eye topically would ensure that the drug would penetrate the ocular tissue simply because the drug was successful when administered systemically. (Id.)

The Court credits Dr. Asbell's testimony on this point over that of Dr. Goren and Dr. Reed.[9] The various experts explained at length the barriers and limitations in the anatomy of the eye to ocular penetration. Thus, a formulator could not reasonably expect a given drug to penetrate ocular tissue without first experimenting with the drug.

There is also no correlation between oral dosing regimens and topical dosing regimens. (Id. at 665.) For example, ciprofloxacin, a fluoroquinolone, is prescribed topically to treat conjunctivitis and orally to treat urinary tract infections. (Id.) The dosage for conjunctivitis requires the patient to administer a drop every four hours, but the dosage for urinary tract infections is a pill taken twice daily. (Id.)

ii. Topical Treatment, Specifically

After a drug is applied topically, the extent and the rate of absorption depend on several factors, including: "the time the drug remains in the cul-de-sac of the eye and precorneal tear film (also known as the residence time); elimination by nasolacrimal drainage; drug binding to tear proteins; drug metabolism by tear and tissue proteins; and diffusion across the cornea and conjunctiva." (PTX 9 at 1626.) The ability of the drug to penetrate the conjunctiva and cornea after topical application is important to the efficacy of the drug. (See PTX 11 at 643.) Topical application of the drug to the eye is ideal as it permits high concentrations of the antibiotic to be obtained at the site of the action, minimizing systemic

[9] Dr. Goren is a practitioner, not a formulator. The Court therefore understands his testimony in this limited context and weighs his testimony regarding the formulation process accordingly.

exposure and side effects. (See id.) However, as discussed, there is no guarantee that a given antibiotic will be able to penetrate ocular tissue.

d. Prior Treatments for Ocular Infections

Dr. Goren and Dr. Mark Abelson -- an expert offered by Plaintiffs who is a practitioner treating patients and a clinical professor of ophthalmology specializing in corneal and external diseases at Harvard Medical School -- testified that as of 1997, the time of the '411 Patent, there were many choices of active ingredients to develop treatments for ocular infections, and there were other systemic and topical antibiotic treatments already available to treat ocular infections. (Trial Tr. at 234, 1085-86, 1094-98, 1111; see also PTX 11; Pls.' Ex. Approved Antibiotics in 1996 (hereinafter "PTX 1056") (sources: PHYSICIAN'S DESK REFERENCE (1996) (hereinafter "PTX 24"); PTX 26, APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCY EVALUATIONS (16th ed. 1996)).) Dr. Goren did not believe that in 1997 there was a long-felt need for a convenient and effective treatment for ocular infections. (Trial Tr. at 233-43.)

i. Fluoroquinolone Antibiotics Versus Macrolide Antibiotics in General

Among the various choices available to researchers at the time of the '411 Patent, the fluoroquinolone antibiotics were considered "the most important new antibiotics in ophthalmology." (PTX 18, Gregory S. H. Ogawa & Robert A. Hyndiuk, The Fluoroquinolones: New Antibiotics in Ophthalmology, 33 INT'L OPHTHALMOLOGY CLINICS 59, 59 (Fall 1993); see also Trial Tr. at 264, 1123; Olivia N. Serdarevic, Role of the Fluoroquinolones in Ophthalmology, 33 INT'L OPHTHALMOLOGY CLINICS 163, 164 (Winter

1993) (hereinafter "PTX 20"); V. Andrews, Antibiotic treatment of ophthalmic infection: new developments, 30 J. OF HOSP. INFECTION 268, 272 (1995) (hereinafter "PTX 35").) They were bactericidal as opposed to bacteriostatic, meaning that they could kill the organisms at issue as opposed to merely keeping the organisms from multiplying, and they were known to be able to act on a broad range of bacteria. (Trial Tr. at 657, 1117-18, 1122-23, 1129; PTX 20 at 163-64.) They were also known to permeate ocular tissues. (See Trial Tr. at 657.)

Macrolides, in contrast, were known to have less favorable properties, such as their narrow spectrum of bacterial activity as compared to other antibiotics. (Id. at 692-93, 1125, 1129-30; Trial Tr. Addendum at 8; WILLIAM O. FOYE ET AL., MEDICINAL CHEMISTRY 791-92 (4th ed. 1995) (hereinafter "DTX 186"); see also Sandra L. Everett et al., An In Vitro Comparison of the Susceptibilities of the Bacterial Isolates from Patients with Conjunctivitis and Blepharitis to Newer and Established Topical Antibiotics, 14 CORNEA 382, 383-85 (July 1995) (hereinafter "PTX 19").) Also, macrolides were generally known to be bacteriostatic and were known to be bactericidal only against very few types of bacteria. (Trial Tr. at 711, 982-83, 1119, 1125, 1127; R. P. Gladue et al., In Vitro and In Vivo Uptake of Azithromycin (CP-62,993) by Phagocytic Cells: Possible Mechanism of Delivery and Release at Sites of Infection, 33 ANTIMICROBIAL AGENTS & CHEMOTHERAPY 277, 280 (Mar. 1989) (hereinafter "PTX 22"); Stephen C. Piscitelli et al., Clarithromycin and azithromycin: New macrolide antibiotics, 11 CLINICAL PHARMACY 137, 139 (Feb. 1992) (hereinafter "DTX 180"); DTX 186 at 792.)

ii. Erythromycin

Erythromycin is the parent drug of the macrolide class. (Trial Tr. at 567, 730.) Erythromycin was available as an ointment to treat ocular infections at the time of the '411 invention. (JTX 101 at 106-07.) It is known to be a bacteriostatic antibiotic; however, it is known to be bactericidal against Streptococcus pyogenes and Streptococcus pneumoniae. (DTX 180 at 139; Trial Tr. at 982.)

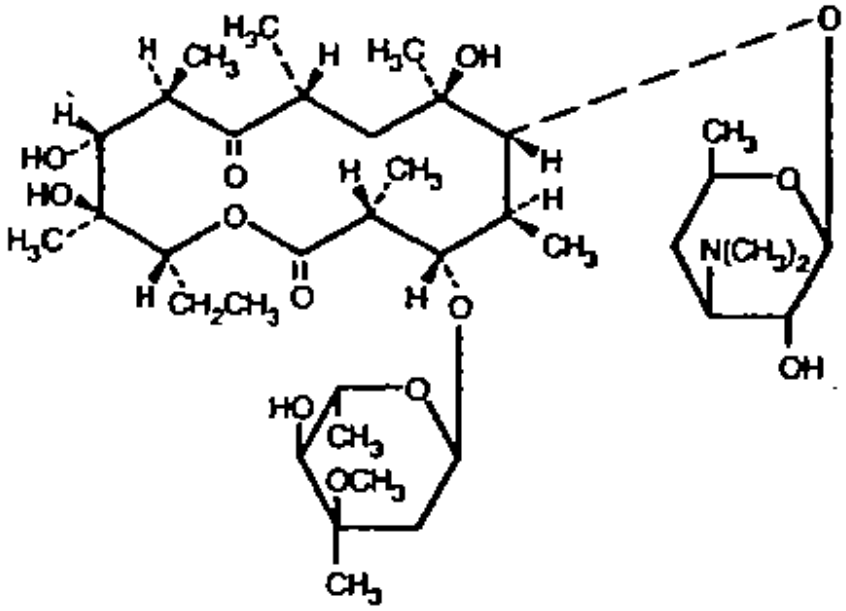
Erythromycin is known to be poorly absorbed in the eye when topically applied. (JTX 101 at 79.) It is therefore frequently dosed four to six times per day as opposed to once daily. (Hisashi Nakagawa, Treatment of Chlamydial Conjunctivitis, 211 OPHTHALMOLOGICA 25, 26 (1997) (hereinafter "PTX 12"); see also Trial Tr. at 240-41, 666, 682.) Dr. Asbell explained that erythromycin needs to be maintained at a high level, and thus, only one dose per day is not adequate to treat the infection. (Trial Tr. at 666.)

Dr. Asbell testified that in the 1990's, erythromycin was not considered a broad-spectrum antibiotic. (Trial Tr. Addendum at 7-8.) An in vitro study concluded that erythromycin was much less effective than several other drugs, including drugs in the fluoroquinolone family. (PTX 19 at 386 tbl. 3.) Dr. Abelson likewise testified in his deposition that erythromycin has fallen out of favor and that neither he nor any other ophthalmologist would prescribe it. (Abelson Dep. Tr. at 77.) He explained that the ointment is "hard to apply, blurs, cakes the lid, falls out, and doesn't have much of a spectrum." (Id.)

Dr. Goren contradicted Dr. Abelson's testimony that the drug has fallen out of favor. He testified that since around 1996, he has prescribed Ilotycin® -- a drug containing the active

ingredient erythromycin that is available to treat ocular infections -- and that he still prescribes it to this day. (Trial Tr. at 234.) He opined that the drug is widely used by others, including his colleagues and his residents over the past twenty years. (Id. at 236.) Dr. Goren also disputed the findings of the in vitro study, stating that while the study indicated that only 49 percent of the organisms in patients were sensitive to erythromycin, real clinical experience contradicts this and suggests that it is much closer to 100 percent. (Id. at 343-44.)

This shows the structural formula of erythromycin:



(PTX 24 at 913.)

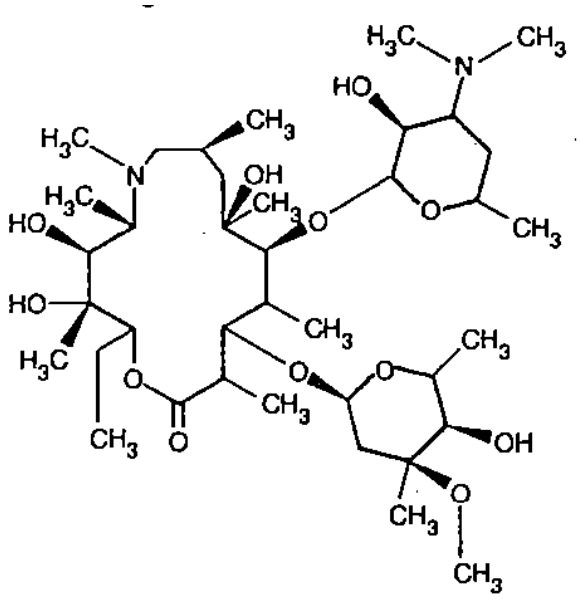
iii. Azithromycin and Zithromax®

Azithromycin is the only FDA-approved azalide antibiotic. (See Trial Tr. at 573.) Azalides are a subclass of macrolides. (See id.) Azithromycin is generally considered bacteriostatic. However, it is known to be bactericidal against Streptococcus pyogenes and

Haemophilus influenzae. (DTX 180 at 139; see also DRUG INFORMATION 257 (Gerald K. McEvoy, ed., 1998) (hereinafter "PTX 39"); Trial Tr. at 711, 982-83.)

The difference between erythromycin and azithromycin appears in a carbonyl group. (Trial Tr. at 569-70.) A carbonyl is removed and nitrogen takes its place "to create a 15-membered macrolide." (Richard M. Shepard & Fred C. Falkner, Pharmacokinetics of azithromycin in rats and dogs, 25 J. OF ANTIMICROBIAL CHEMOTHERAPY 49, 49 (1990) (hereinafter "DTX 184"); see also Trial Tr. at 570; DTX 180 at 138.) "This structural modification protects azithromycin from breakdown by acid, as well as substantially increasing tissue penetration and elimination half-life." (DTX 180 at 138; see also DTX 186 at 793; Trial Tr. at 714.) The longer half-life, which results in longer residence time in tissues, permits "greater and longer tissue penetration, allowing once-a-day dosage," thereby alleviating some patient-compliance concerns. (DTX 186 at 793; see also DTX 180 at 138, 148; DTX 185, H. Lode, The Pharmacokinetics of Azithromycin and Their Clinical Significance, 10 EUR. J. OF CLINICAL MICROBIOLOGY & INFECTIOUS DISEASES 807, 811 (Oct. 1991).) This knowledge was based on the oral administration of azithromycin. (See, e.g., DTX 184 at 56.) The consensus by experts is that azithromycin has more wide-ranging penetration and greater benefits than erythromycin and other macrolide antibiotics. (See PTX 39 at 257; DTX 180 at 137 (Abstract), 143; DTX 184 at 49-50, 57-58; Trial Tr. at 184-85.)

This shows the structural formula of azithromycin:



(PTX 24 at 1944.)

Azithromycin is the active ingredient in Zithromax®, which was first approved for use by the FDA in the early 1990's. (See id. at 1944; Trial Tr. at 179, 557, 559.) Zithromax® is orally dosed, and it is indicated for a variety of "mild to moderate infections". (PTX 24 at 1944-45.) According to Dr. Goren, by 1996, Zithromax® was widely prescribed in the United States. (Trial Tr. at 179-80.)

(a) Oral Administration of Azithromycin

The prior art around the 1996 priority date of the '411 Patent pointed away from the topical application of azithromycin and instead favored the oral administration. Oral use of azithromycin worked through a unique process called phagocytosis, which was bloodstream dependent and was not available or relevant for topical application. (Id. at 329-31, Trial Tr. Addendum at 3; PTX 22 at 281.) Additionally, when administered systemically,

azithromycin could be absorbed by the bloodstream and carried to the lacrimal gland, allowing the drug to be secreted into tears and carried to the infected tissue. (Trial Tr. at 330-31.) Following the oral application of azithromycin, the drug is rapidly absorbed and carried throughout the body, resulting in high concentrations of the drug in the tissues. (Id. at 575.) According to Dr. Reed, "this drug loves to go into the tissue" and stay there for a long period of time. (Id. at 575, 579, 584-86, 721; see also Denis M. O'Day et al., Ocular Pharmacokinetics of Orally Administered Azithromycin in Rabbits, 10 J. OCULAR PHARMACOLOGY 633, 636 (1994) (hereinafter "DTX 183"); DTX 184 at 49, 56.)

Studies show that orally administered azithromycin has been remarkably effective in treating trachoma as compared to conventional treatments, and it could transform programs to control trachoma. (PTX 135, R.L. Bailey et al., Randomised controlled trial of single-dose azithromycin in treatment of trachoma, 342 THE LANCET 453, 453-56 (1993); Trial Tr. at 426.) Single daily dosing of oral azithromycin has been preferred over conventional topical treatments requiring drugs to be administered multiple times a day, which results in discomfort and blurred vision for the patient. (DTX 230, C.R. Dawson et al., A Comparison of Oral Azithromycin with Topical Oxytetracycline/Polymyxin for the Treatment of Trachoma in Children, 24 CLINICAL INFECTIOUS DISEASES 363, 367 (1997).) Another positive of oral dosing of azithromycin to treat trachoma is that there are few, if any, serious side effects. (Trial Tr. at 491-92.) Experts on both sides, however, have agreed that, because trachoma is a systemic illness, the oral dosing of azithromycin to treat trachoma is not

relevant to topical formulations of azithromycin. (See id. at 326, 492-93, 685, 1068, 1343-44.)

(b) Expectation that Azithromycin Would Permeate Ocular Tissues

According to Dr. Reed, a number of factors affect whether a substance may penetrate the cornea, including the molecular weight, the solubility, the partition coefficient, and ionization. (Id. at 965-66, 1018-19.)

(i) Solubility

With respect to solubility, a molecule must be in a solution to effectively penetrate through tissue. (Id. at 838, 966.) Solubility measures "how many molecules you can get to go into the solution." (Id. at 966.) A higher solubility results in a higher concentration of the drug, and higher concentrations provide greater "driving force" for penetrating the cornea. (Id.)

Because tear fluid is water, issues of solubility arise in the context of the potential for a drug's topical application. (See id. at 1012-14.) While Dr. Reed testified that a POSITA would believe that azithromycin was soluble in water, other sources indicate that azithromycin and all macrolides are known to be insoluble in water. (See id. at 741-42, 1012-13; Azithromycin, EUROPEAN PHARMACOPOEIA 5.0 1039, 1039 (hereinafter "PTX 36"); PTX 35 at 273.) Azithromycin specifically and macrolides in general are prone to hydrolysis, or a breakdown of the chemical structure in water. (JTX 101 at 42-43, 52, 56, 59.) These insolubility concerns indicate "that [macrolides] will remain a poor choice for the topical treatment of serious infection, as the rate of drug delivery from an eye ointment is not

sufficiently high to achieve consistently adequate tissue concentrations." (PTX 35 at 273.) Dr. Imran Ahmed testified that the potential instability of azithromycin can be controlled somewhat by refrigerating the product, as "hydrolytic stability is usually temperature dependent." (JTX 101 at 56.)

(ii) Partition Coefficient – Log P

Log P, or the partition coefficient, is a measure of lipophilicity, or "a measure of a molecule's preference to be in the lipid environment." (Trial Tr. at 717-18, 833-34, 966.) This value measures the drug's affinity for water over another substance -- in this case, organic tissue. (Id. at 717-18, 838-39.) The log P or partition coefficient, along with molecular weight, is used to determine whether a given molecule will penetrate ocular tissues. (Id. at 838.)

Sandoz's expert Dr. Reed testified that, generally, as log P increases (or the more "lipid loving" a substance is), ocular tissue permeability increases, and this correlation is quite strong. (Id. at 724-27, 1022.) Dr. Reed explained that the log P of azithromycin is 4.02, and the log P of erythromycin is only 3.06. (Id. at 725.) This would indicate that azithromycin is better suited to penetrate ocular tissue. However, Plaintiffs' expert Dr. Vincent Lee, a doctor of pharmaceutics who was admitted as "an expert in ophthalmic pharmaceutical formulation design, development, and drug delivery," stated that azithromycin's log P of 4 was outside of the optimal log P range of 2 to 2.5 for best permeability, which would discourage a POSITA from using azithromycin when seeking to penetrate tissue. (Id. at 1263-65, 1286-87.)

(iii) Molecular Weight

Molecular weight affects both movement between cells (paracellular movement) and movement through cells (transcellular movement). (Id. at 1032-33.) Substances with a greater molecular weight have more difficulty penetrating cells than substances with a lower molecular weight. (Id. at 1017-18.)

The molecular weight of azithromycin is 749 daltons. (James W. McFarland et al., Quantitative Structure – Activity Relationships Among Macrolide Antibacterial Agents, 40 J. OF MED. CHEMISTRY 1340, 1341 tbl. 1 (1997) (hereinafter "DTX 181"); see also Trial Tr. at 840, 842.) Sandoz's expert Dr. Reed acknowledged that a POSITA would be concerned about azithromycin's ability to penetrate ocular tissue given its large molecular weight. (Trial Tr. at 843-44.) Despite this, he said that other ophthalmic treatments with similar molecular weights (like erythromycin at 735 daltons) or greater molecular weights have been able to penetrate ocular tissue. (See id. at 843-44; DTX 181 at 1341 tbl. 1.)

(iv) Ionization/Charge

At the time of the '411 Patent, it was well known in the field that non-ionized, or uncharged, molecules have an easier time penetrating ocular tissue than ionized, or charged, molecules. (Trial Tr. at 717, 1018-19, 1277-78; DTX 84 at 84.) Azithromycin, however, was known to be charged when in tear fluid, which has a pH close to 7. (See Trial Tr. at 1019-20, 1279-80.)

iv. Other Known Antibiotics

As of the time of the patenting of the '411 invention in December of 1997, there were "many hundreds" of choices for active ingredients to consider using in topical ophthalmic antibiotic formulations. (Id. at 1111.) There were at least 100 FDA-approved antibiotics. (Id. at 1096-97; PTX 1056.) A formulator could obtain lists of such approved antibiotics by consulting the Physician's Desk Reference ("PDR"), which is published annually. (Trial Tr. at 662.) Formulators could also attempt to work with an FDA-approved drug to formulate it for uses other than those previously approved by the FDA. (Id. at 189-91, 606-07.) Additionally, in 1997, there were new antibiotics still undergoing clinical trials. (Id. at 1098-1103.) Formulators also could combine known antibiotics, and the resulting formulations could potentially have a greater spectrum of bacterial coverage than either of the individual components, working alone. (Id. at 1103-04, 1107.) Known antibiotics could be combined with another active ingredient, such as a steroid. (Id. at 1105-07.) Moreover, existing topical treatments could be improved by, for example, reducing the dosage and frequency of administration. (Id. at 1108-09.) And finally, using a prodrug -- a molecule that is not able to penetrate tissue on its own but can be turned into an active drug when acted upon by the human body -- of a known antibiotic was another option for formulators. (Id. at 1109-11.)

e. The '411 Invention – Topical Administration of Azithromycin

Dr. Ahmed is the inventor named in the '411 Patent. Dr. Ahmed testified that his initiative in developing the '411 invention was not to develop "specific formulations," but

rather, "to look at the feasibility of delivery of azithromycin to the eye . . . in a topical form." (JTX 101 at 15-16.)

He testified that he determined the amount of the active ingredient in his invention -- .5% azithromycin (see DTX 1 at col. 6, lines 7-8 (Claim 6 of the '411 Patent)) -- after referencing, as a starting point, literature reporting on the ranges of other antibiotics used in topical formulations. (JTX 101 at 32-33.) Dr. Ahmed chose other elements based on how they would be tolerated in the eye. (Id. at 33-34.) He determined the exact formulation of non-active ingredients based on "ratios that are used in formulations that are known to be well tolerated in marketed products." (Id. at 34.)

Dr. Ahmed was concerned about the stability of any substance containing azithromycin dihydrate in water given that azithromycin and macrolides are prone to hydrolysis; however, this could be somewhat controlled with refrigeration. (Id. at 42-43, 56.) Dr. Ahmed used erythromycin and the PDR as a reference in developing the '411 invention. (Id. at 123, 126-29.) After animal testing, Dr. Ahmed concluded that the invention could be dosed once daily. (Id. at 65-66.)

f. Issuance of the '411 Patent

The '411 Patent, filed on November 25, 1998, is titled "Method of Treating Eye Infections with Azithromycin," and it lists Dr. Ahmed as the inventor and Pfizer as the assignee. (DTX 1 at [22], [54], [73], [75].) The relevant claims of the patent are as follows:

> **1.** A method of treating an ocular infection, comprising topically administering to an eye of an animal in need of such treatment an ocular infection-treating amount of azithromycin.

> **2.** A method as defined in claim **1** wherein said azithromycin is present in a composition comprising a pharmaceutically acceptable topical vehicle at a concentration of from 0.1 to 2.5 weight percent.

(Id. at col. 5 lines 8-15.)

> **3.** A method as defined in claim **2**, wherein said composition is administered once daily.

(Id. at col. 6, lines 1-2.)

> **5.** A method as defined in claim **2**, wherein said azithromycin concentration is from 0.2 to 2.0 weight %.

(Id. at col. 6, lines 5-6.)

Plaintiffs have alleged that Sandoz's ANDA product will infringe claim 3 and claim 5.

g. Evidence of Motivation to Combine References

As discussed supra in section II.C.1.d.iii, at the time of Dr. Ahmed's '411 invention in 1997, ophthalmologists had found the oral administration of azithromycin to be successful, and they believed that the properties of azithromycin, including its high molecular weight and instability in water, rendered it an unlikely candidate for successful topical administration.

Sandoz's expert Dr. Reed, however, opined that a POSITA in 1996 would "have been motivated to try azithromycin as a topical antibiotic" because it "is the newer iteration of an earlier successful antibiotic" (i.e., erythromycin), and the data indicated that azithromycin was more likely to be successful than erythromycin. (Trial Tr. at 821-22.)

Sandoz presented some additional evidence that some researchers had considered developing topical treatments containing azithromycin for ocular infections at the time of Dr. Ahmed's '411 invention. On June 30, 1997, the World Health Organization ("WHO") held

its first meeting of the WHO Alliance For the Global Elimination of Trachoma in Geneva, Switzerland (hereinafter "the WHO Meeting"). (Id. at 436.) Dr. West, who attended the WHO Meeting, described it as "a format" whereby researchers, countries, and non-governmental organizations could talk about their progress on anything "that related to efforts to eliminate trachoma." (Id. at 436, 440-41.) The WHO Meeting also generated a report (hereinafter "the WHO Report"), which provided details on the status of current trachoma treatments and ongoing research in the field of trachoma treatments. (See WORLD HEALTH ORGANIZATION, REPORT OF THE FIRST MEETING OF THE WHO ALLIANCE FOR THE GLOBAL ELIMINATION OF TRACHOMA (1997) (hereinafter "DTX 216").)

According to Dr. West, Dr. Chandler Dawson, a Professor of ophthalmology whom Dr. West described as a "giant[] in the trachoma field," gave a fifteen- to twenty-minute presentation at this meeting about topical azithromycin. (Trial Tr. at 450-51, 456.) Dr. West explained that Dr. Dawson "presented what I interpreted to be his idea for creating a topical form of azithromycin for the treatment of trachoma. He outlined, as I recall, some advantages and disadvantages and then talked about some of the ways that this might go forward." (Id. at 451.) The positives (as recalled by Dr. West from Dr. Dawson's presentation) were: the potential for once-daily dosing; the reduction of the resistance of other bacteria; and the treatment of inactive trachoma, which systemic treatments could not do. (Id. at 458-60; see also DTX 216 at 16.) The negatives were that: ointments are difficult to apply; topical dosing could be expensive particularly for large-scale distribution; topical treatments would not affect extraocular reservoirs of infection; and topical treatments would not benefit from the unique,

blood-stream dependent process of phagocytosis found with systemic dosing. (Trial Tr. at 455, 458, 1343-45; see also DTX 216 at 16.) The failure of topical treatments to affect extraocular reservoirs meant that the eye could become reinfected. (Trial Tr. at 492-93.)

Dr. Dawson also explained that successfully formulated azithromycin eye drops need to be: (1) stable for long periods of time (i.e., a long shelf-life) in tropical and sub-tropical climates; (2) well tolerated; (3) effective to treat both trachoma and other bacteria that present as conjunctivitis; and (4) easily available, and cost-effective for trachoma-control programs. (See id. at 459-60, 1345-47; DTX 216 at 17.)

Dr. West stated that the reaction to the idea of topically dosing azithromycin at the 1997 WHO Meeting was "muted." (Trial Tr. at 455.) The focus at the meeting "was directed towards the possibility of a donation program for azithromycin" for systemic dosing. (Id.)

Plaintiffs moved before trial to prevent Sandoz from entering the WHO Report of the WHO Meeting (DTX 216) at trial. (See dkt. entry nos. 95 & 96, Pls.' Mot. in Limine No. 4.) The Court granted the motion in limine, directing that the WHO references were not admissible as prior art. (Dkt. entry no. 153, 7-12-13 Order.) At trial, over Plaintiffs' objection, the Court permitted Sandoz to admit DTX 216 on the issues of motivation to combine references, long-felt need, and reasonable expectation of success. (Trial Tr. at 436-38.) Plaintiffs also objected to Dr. West's testimony of what was said at the WHO Meeting, but the Court allowed Dr. West to testify regarding her recollection of the Meeting. (Id. at 450-53.)

The Court concludes that Dr. West's testimony regarding what persons in the field knew about topical treatments of azithromycin for trachoma is admissible. The Court finds that her testimony is not hearsay, as she testified only to her mental impressions following the presentation. Even if her testimony is hearsay, it is admissible under the residual hearsay exception, Federal Rule of Evidence 807, as the WHO Report provides the requisite indicia of reliability.

The Court also reaffirms its prior ruling that the WHO Report (DTX 216) is not prior art because the Court finds that Sandoz could not prove it was published or publicly accessible under 35 U.S.C. § 102(b). See In re Lister, 583 F.3d 1307, 1311 (Fed.Cir. 2009) (document is not a "printed publication" under § 102(b) where evidence does not establish that it was sufficiently publicly accessible before the critical date); In re Hall, 781 F.2d 897, 899 (Fed.Cir. 1986) ("The proponent of the publication bar must show that prior to the critical date the reference was sufficiently accessible, at least to the public interested in the art, so that such a one by examining the reference could make the claimed invention without further research or experimentation."). First, the copyright page of the Report itself states, "[t]his document is not a formal publication of the World Health Organization." (DTX 216.) Moreover, Sandoz failed to carry its burden of demonstrating that these references were publicly disseminated before the critical date. Sandoz neither demonstrated that the WHO Report was published in a known journal nor provided evidence of its public accessibility. The mere existence of the WHO Report prior to the critical date is insufficient to demonstrate that it was publicly available. See Lister, 583 F.3d at 1317.

Even assuming arguendo that the WHO Report was published by the critical date, Dr. West's testimony and the WHO Report were only weak evidence of motivation to combine references and long-felt need, and in many ways, they taught away from the topical use of azithromycin. The positives for Sandoz's position regarding the topical use of azithromycin to treat trachoma include: the potential for once-daily treatment; the avoidance of systemic treatment of children with inactive trachoma; the reduced rate of resistance in other bacteria; the potential for treatment by family members; and the potential for a reduction in the cost of azithromycin. (DTX 216 at 16.) The negatives for Sandoz's position, and therefore the positives for Plaintiffs' position, include: the difficulties of applying an ointment; the failure of a topical treatment to affect extraocular infections; the potential expense of large-scale distribution; the absence of the unique, blood-dependent process (phagocytosis) present with systemic administration; and the fact that efficacy and dosing would need to be determined because no product is available for this purpose. (Id.) The United States Court of Appeals for the Federal Circuit acknowledged these negatives in a related matter, and stated that the WHO Report details "a number of objections to such [a trachoma] treatment." Dawson v. Dawson, 710 F.3d 1347, 1348 (Fed.Cir. 2013). The WHO Report's outlook for topical azithromycin is neutral at best.

The relevancy of the WHO Report and Dr. West's testimony to the validity of the patents at issue is also questionable. Experts for both parties agreed that the treatment of trachoma is not relevant to whether azithromycin would work topically because trachoma is a systemic disease. (See Trial Tr. at 326, 492-93, 685, 1068, 1343-44.) Furthermore, the

examiner was aware of the existence of the WHO Meeting and/or Report during the review of the '411, '113, and '443 Patents, and the examiner approved the patents as they exist today. (See DTX 1 at [56] (other publications); DTX 2 at [56] (other publications); DTX 3 at [56] (other publications).) Notably, the examiner denied other claims for these patents based on the WHO references; thus, the fact that the examiner approved the remaining claims demonstrates that the examiner did not find these remaining claims to be obvious on the basis of the WHO references. (See DTX 6, File History of Patent Application for '113 Patent at 73, 82-83, 89-90.) Therefore, the inclusion or exclusion of Dr. West's testimony and the WHO Report do not change the Court's conclusions.

h. Reasonable Expectation of Success

As discussed supra in section II.C.1.a-c, penetration of ocular tissue is essential for the successful treatment of ocular infections, and penetration is complex and difficult to achieve. (See Trial Tr. at 285, 615-17, 626, 628-29, 653, 957-58, 962-65, 1134-42; DTX 84 at xv, 22.) The characteristics of azithromycin, such as its instability in water and its high molecular weight, present particular challenges to such penetration. (See supra section II.C.1.d.iii.) Additionally, Dr. Asbell testified that azithromycin has a narrow spectrum of bacterial coverage. (Trial Tr. App. at 7-9.)

During the development of the '411 invention, Dr. Ahmed believed, based on his experience with ophthalmic formulations, that there was a "low probability" that azithromycin would work as a topical treatment for ocular infections. (JTX 101 at 78.) Dr. Ahmed wrote in his lab notebook, "Azithromycin is a macrolide antibiotic effective against a variety of

microorganisms, including clamydiae [sic]. It is proposed ~~expected~~ that a topical presentation of azithromycin may be effective in treating clamydial [sic] trachomatis infection in neonates." (DTX 14, Pfizer Notebook No. 17529, issued to Imran Ahmed, filed 10-24-95, at 72.) Dr. Ahmed explained that he crossed out expected because expected meant to him "something that you know will work. So that was a correction that reflects that the work hasn't been done for me to expect anything." (JTX 101 at 78.)

Dr. Reed opined, on the other hand, that a POSITA would have had a reasonable expectation of success for the formulation in the '411 Patent because azithromycin is a known antibiotic that had shown incredible tissue retention, high topical concentrations, and wide spectrum activity. As a result, Dr. Reed would have expected that it could be dosed once daily. (See Trial Tr. at 806-08, 814, 823.)

i. Secondary Considerations

i. Unexpected Results

Sandoz's experts Dr. Reed and Dr. Goren testified that higher concentrations of azithromycin would have been expected after topical application rather than after oral administration. (Id. at 231, 646-47, 939-40.) According to Dr. Reed, "the reason we have ophthalmic medications is because you can get higher concentrations at the site of the action." (Id. at 939-40.) Moreover, Dr. Reed testified that azithromycin "loves to go into the tissue" and remain there for a long period of time. (Id. at 575, 579.) Dr. Asbell, on the other hand, disagreed that such high concentrations would be expected, given the eye's external barriers to penetration and the experience with fluoroquinolones. (Id. at 643, 646-47.)

ii. Long-Felt Need for Topical Ophthalmic Formulations of Azithromycin

There was conflicting evidence at trial regarding whether there was a long-felt need for topical ophthalmic formulations of azithromycin. Dr. West did not feel that there was a long-felt need for a new topical treatment to treat trachoma, regardless of the active ingredient in any formulation. (See id. at 475-80, 485, 498-99.) She explained that the reaction at the WHO Meeting to the potential of formulating topical treatments of azithromycin to treat trachoma was "muted," and the focus of the meeting was on a donation program of azithromycin for oral treatments, which satisfied the majority of needs. (Id. at 455, 479-80.) Moreover, ophthalmologists already had a topical treatment, topical tetracycline, which was WHO recommended and very inexpensive. (Id. at 478.) Dr. Goren also testified that the introduction of AzaSite® has not changed the standard of care for conjunctivitis and that ophthalmologists have continued to use drugs that pre-existed AzaSite® to treat bacterial conjunctivitis. (Id. at 233-43.)

Dr. Asbell opined, in contrast, that it "definitely" would have been beneficial in 1997 to have a topical ophthalmic antibiotic with a wide spectrum of activity that could be dosed once daily because it would be much easier to administer. (Id. at 670; Trial Tr. App. at 7.)

j. Dr. Reed's Patent

Dr. Reed's testimony regarding the obviousness of the '411 Patent is undermined by his own prior conduct. Dr. Reed had a patent in 1994 for topical ophthalmic treatments. (U.S. Patent No. 5,422,116 (filed Feb. 18, 1994) (hereinafter "PTX 123').) While Dr. Reed claimed 24 antibiotics, including erythromycin, Dr. Reed did not include azithromycin on his

list, even though it had been known since 1984 and had been approved for oral use by the FDA in 1991. (Id. at col. 13, lines 33-41; Trial Tr. at 1041-46.)

k. Facts Related to Hindsight Analysis

Plaintiffs have criticized Dr. Reed's testimony and have asserted that he improperly employed a hindsight analysis. (Pls.' Post-Trial Br. at 7.) Dr. Reed admittedly reviewed the '411 Patent and then reviewed related prior art. (Trial Tr. at 547, 950-51.) "I focused on learning more about azithromycin because the patents were in regard to azithromycin." (Id. at 547.) Dr. Reed only looked at data for azithromycin and macrolides and did not compare it to data for any other similarly-used antibiotics. (Id. at 546-47, 567-74, 710, 950-51, 995.) Even with this narrow focus, Dr. Reed admitted that none of the sources he "reviewed disclosed topical ophthalmic azithromycin compositions" before the '411 Patent. (Id. at 953.)

2. Framing the Issue

Before addressing the validity of claim 3 and claim 5 of the '411 Patent, the Court must define "the design need or market pressure" faced by POSITAs as of December 2, 1996, the priority date for the '411 Patent. (See supra n.8.) See KSR, 550 U.S. at 418-19 (noting the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" because "claimed discoveries almost of necessity will be combinations of what . . . is already known"); see also Metso Minerals, Inc. v. Powerscreen Int'l Distrib., Ltd., Nos. 11-1572, 12-1168, 12-1169, 2013 WL 1969309, at *7 (Fed.Cir. May 14, 2013). Defining those needs and

pressures sets the stage for analysis relating to the obviousness or nonobviousness of the claims at issue in the '411 Patent.

The parties frame the issues that ran through this trial in very different ways. (See Closing Args. Tr. at 5 (describing the proceedings as a "tale of two trials").) Sandoz argues that the question facing a POSITA in December of 1996 was whether one could treat conjunctivitis with a topical ophthalmic formulation of azithromycin. (See Sandoz's Post-Trial Br. at 1, 10-12, 16 (arguing that POSITAs would have considered it obvious to use a topical formulation azithromycin to treat conjunctivitis).) Plaintiffs, on the other hand, argue that Sandoz has used the '411 Patent as a guide and thus, improperly, has framed the question through the lens of hindsight. (See Pls.' Post-Trial Br. at 1-2, 5-6.) They describe Sandoz's framing and analysis as "fundamentally flawed." (Id. at 1.) Plaintiffs argue that the question before the Court is better framed by the desire of POSITAs, in December of 1996, to develop improved topical treatments for ocular infections. (Id.) They argue that the Court must stand in the shoes of such a person and determine -- with knowledge of the many hundreds of antibiotic options that one could research and develop -- whether it would have been obvious to develop a topical ophthalmic formulation that contained azithromycin.

The Court agrees with Plaintiffs. At the time of the '411 invention, there were many options available to a formulator when considering topical ophthalmic treatments. As described, a researcher had a number of options to consider: FDA-approved drugs for purposes other than the approval given by the FDA; combinations of antibiotics with each other and with other active ingredients; antibiotics that were in the pipeline; improvements to

existing topical treatments; and even prodrugs. (See supra section II.C.1.d.iv.) Aside from the variety of options, research pertaining to azithromycin and macrolides in general discouraged their use as topical ophthalmic treatments. They were known to be bacteriostatic, to have a limited spectrum of activity, and to require multiple doses per day to penetrate tissue. (See supra section II.C.1.d.) In contrast, in the 1997 timeframe, fluoroquinolones were believed to be more favorable in that they were bactericidal and had a broad spectrum of bacterial activity. (See id.) In addition to knowledge regarding specific antibiotics and treatments, researchers were well aware of the difficulties with ocular penetration given the eye's defense mechanisms and the unique balance of log P, molecular weight, solubility, and charge that would render one antibiotic a good candidate for topical application. (See supra section II.C.1.a,c,d.) Notably, azithromycin's characteristics indicated that it was not a good candidate. (See supra section II.C.1.d.iii(b).)

For these reasons, the issue as framed by Sandoz is too narrow in that it limits its scope to conjunctivitis and to azithromycin. The issue, as advanced by Plaintiffs, is the desire to develop a topical treatment for ocular infections.

3. Substantive Analysis

Sandoz argues a POSITA, "[b]ased on the prior art and on common sense," would have been motivated to make the claimed inventions, and held a reasonable expectation of success. (See Sandoz's Post-Trial Br. at 16-27.) Sandoz relies on two sets of prior art teachings, i.e., those related to: (1) the properties of orally administered azithromycin; and (2) topically administered erythromycin. (See id. at 16-19; Pls.' Post-Trial Br. at 13.) The Court

will thus consider whether a POSITA would have been motivated to combine such references to make a topical ophthalmic formulation of azithromycin and whether such person would have had a reasonable expectation of success.

a. Sandoz's Arguments in Favor of Motivation and Reasonable Expectation of Success

Sandoz argues that a POSITA would have been motivated to make a topical ophthalmic formulation of azithromycin for several reasons. First, the prior art taught that azithromycin, when dosed orally, was an important drug for the treatment of trachoma. (Sandoz's Post-Trial Br. at 16-18.) An oral dose of azithromycin was as effective at treating trachoma as the traditional regimen of topical tetracycline. (Id. at 16.) A researcher would expect a topical application of the drug to have a greater spectrum activity than when dosed orally, given the high concentrations typically achieved by topical administration. (Id. at 22-23.) Second, azithromycin had a demonstrated affinity for ocular tissue and a prolonged half-life. (Id. at 16-9.) These propensities to accumulate in tissue created the expectation of success of a topical treatment of azithromycin. (Id. at 20-21.) Third, topical antibiotic treatments for ocular infections were known to have advantages over systemic treatments. (Id. at 17-18.) And finally, erythromycin was effective when dosed topically, and azithromycin was, in many respects, a newer and better version of erythromycin; thus, a POSITA would have an expectation of success of a topical treatment of azithromycin given its chemical characteristics. (Id. at 18-20, 25-27.)

b. Plaintiffs' Arguments Against Such Motivation and Reasonable Expectation of Success

Plaintiffs argue that a POSITA, when considering options for new topical ophthalmic antibiotic formulations, would not have considered azithromycin. First, prior art references discouraged use of macrolides. (Pls.' Post-Trial Br. at 9-13.) Second, a POSITA would not have inferred that azithromycin was a good choice for topical administration merely because it worked well when dosed orally, and Sandoz failed to prove any correlation between the effectiveness of an oral dose of an antibiotic and a topical dose of that same antibiotic. (Id. at 15-23.) This is particularly true given the differences in anatomy between the stomach and the eye. (Id. at 15-19.) The ability of the drug to penetrate the eye when applied topically could not be predicted based on the drug's properties after systemic administration. (Id. at 15-23.) Plaintiffs also argue that the characteristics of azithromycin, including its molecular weight and insolubility, rendered it an unlikely candidate for crossing the natural ocular barriers. (Id. at 14-15, 23-28.)

Moreover, oral dosing of azithromycin relied on phagocytosis, the blood mechanism through which the drug was delivered to the tissues following oral dosing, and phagocytosis is bypassed with topical dosing. (Id. at 19-21.) Sandoz responds to this by asserting that phagocytosis is not the only means of delivery to the eye. (Sandoz's Post-Trial Br. at 18.)

Plaintiffs also argue that there are many other options for a topical ophthalmic, yet Sandoz fails to explain why a POSITA may have chosen azithromycin over those options. (Pls.' Post-Trial Br. at 7, 12.) A POSITA would have formulated other drugs including fluoroquinolones as topical ophthalmics before formulating azithromycin, because

fluoroquinolones were known to be a better option than azithromycin. (Id. at 9-13.) Plaintiffs assert that the prior art taught away from azithromycin's use as a topical treatment because azithromycin's characteristics indicated that it would have difficulty penetrating ocular tissue. (Id. at 23-26.) Plaintiffs emphasize that Sandoz's own expert, Dr. Reed, considered other drugs for his invention, but did not consider azithromycin. (Id. at 28-29.)

Plaintiffs' final argument on this issue is that Sandoz limits its inquiry to treatment options for conjunctivitis, which Sandoz alleges is "not difficult." (Id. at 18-19.) This is improper because the '411 Patent's claims relate to ocular infections, which can occur in any part of the eye, and Sandoz fails to consider the likelihood that an infection could spread from the conjunctiva to the cornea. (Id.)

c. Conclusions on Motivation and Reasonable Expectation of Success

The Court finds that Sandoz has failed to carry its burden to demonstrate that a researcher would be motivated to combine references to create an azithromycin topical treatment for ophthalmic infections and would have had a reasonable expectation of success in doing so. Thus, Sandoz has failed to prove obviousness. See Procter & Gamble, 566 F.3d at 994.

Claim 3 of the '411 Patent claims once-daily dosing of a topical ophthalmic formulation of azithromycin at a concentration of 0.1 to 2.5 weight percent. (DTX 1 at co1. 6, lines 1-2.) Sandoz relies on prior art references showing that azithromycin could be dosed once daily when orally/systemically administered. But -- as demonstrated in prior art references concerning ciprofloxacin -- there is little or no correlation between oral dosing

regimens and topical ophthalmic dosing regimens. (Trial Tr. at 665-66.) Sandoz improperly concludes that the once-daily oral dosing of azithromycin, which was delivered to the eye at least in part through the mechanism of phagocytosis, correlated with topical dosing to parts of the eye that were known to be avascular. But there appears to be little or no relationship between phagocytosis and topical delivery of antibiotics. (See, e.g., id. at 329-30, 1152.) Nothing in the record suggests that the delivery of azithromycin to ocular and other tissues through phagocytosis demonstrates that azithromycin could permeate conjunctival and corneal tissues when applied topically.

With respect to claim 3 and claim 5 of the '411 Patent, Sandoz, moreover, appears to have engaged in improper hindsight analysis in that it used the '411 Patent as a guide and merely compared azithromycin to other macrolide antibiotics. Under the body of post-KSR hindsight law, Sandoz's failure to consider the suitability of azithromycin by comparison to other non-macrolide antibiotics is inappropriate. Ortho-McNeil Pharm., 520 F.3d at 1364 (hindsight is "always inappropriate for an obviousness test"); Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1138 (Fed.Cir. 1985) ("The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time."). Sandoz's experts, particularly Dr. Reed, failed to consider any of the many other options of compounds known to ophthalmic art and the various potential ways to formulate them. (See Trial Tr. at 546-47, 710, 950-53, 1094-1111, 1315-21.) For example, fluoroquinolones were known to have more favorable qualities for ophthalmic treatments than macrolides in that they were bactericidal and could act on a broad range of bacteria. (Id. at 657, 1122-30, 1133.)

A researcher also could have experimented with existing antibiotics, combinations of existing antibiotics, new ingredients and existing antibiotics, and antibiotics in the pipeline, and could have improved existing topical ophthalmic treatments. (See id. at 1094-1110.) The availability of the innumerable other options is far from the "finite number of identified, predictable solutions" necessary to demonstrate obviousness. KSR, 550 U.S. at 421. This improper hindsight analysis alone appears to control the action because Sandoz bears and has failed to carry its burden of proof.

The Court, however, has considered the totality of the evidence and need not rely on hindsight analysis to reach the earlier-stated conclusion that the claimed inventions described in claim 3 and claim 5 of the '411 Patent are not obvious. Azithromycin's characteristics taught away from its use as a topical ophthalmic treatment, and thus, Sandoz is unable to carry its burden of demonstrating that a researcher would have had a reasonable expectation of success. It is undisputed in the record that a POSITA would prefer to formulate an antibiotic that would permeate both conjunctival tissues and corneal tissues. These tissues are close to each other and bacteria are known to spread. (Trial Tr. at 207-08, 650-53, 1133-34, 1150.) Azithromycin, without experimentation, would have appeared to be a poor choice for penetration of corneal tissue, and thus, the prior art taught away from using azithromycin as a topical ophthalmic treatment. Azithromycin was known to be a large molecule with a weight of 749 daltons, and poor corneal penetration had been observed with drugs of molecular weights over 500 daltons. (Id. at 1273-76; DTX 84 at 32.) Moreover, ophthalmic drugs need to dissolve in tear fluid to be effective, and azithromycin was known to be "practically"

insoluble in water. (PTX 36 at 1039; Trial Tr. at 1013-14, 1271-73.) And finally, charged molecules have difficulty penetrating ocular tissue, and azithromycin was known to be charged in water. (Trial Tr. at 717, 1018-19, 1277-80.) These factors would have discouraged an ordinary researcher from attempting to formulate a topical ophthalmic treatment using azithromycin, and a researcher would not have had a reasonable expectation of success of any such formulation. Fluoroquinolones, by contrast, were known to penetrate ocular tissues.

A POSITA would also prefer to formulate an antibiotic that has a broad spectrum of activity. (Id. at 1122, 1129-30.) While azithromycin had a greater spectrum of activity than erythromycin, the fluoroquinolones had a greater spectrum of activity than azithromycin and were known to be effective. (Id. at 657, 1117-19, 1122-25, 1128-30, 1133; PTX 19.) Because the prior art taught away from using azithromycin, a POSITA would not have had a reasonable expectation of success and would not have considered the claimed inventions to be obvious.

This conclusion is supported by Dr. Reed's patent. Dr. Reed -- when working as a formulator -- patented an ophthalmic vehicle for medicaments. But, at that time, he (1) did not review the literature that was available pertaining to azithromycin, and (2) did not include azithromycin in his patent's list of medicaments but listed erythromycin. (PTX 123 at col.13 ll.33-41; Trial Tr. at 1041-46.) As a POSITA, he appears not to have considered azithromycin. This undermines Sandoz's contention that the '411 Patent was obvious, or that

a POSITA would have had a reasonable expectation of success in using azithromycin as a topical ophthalmic treatment.

Consideration of the WHO references does not change the result. Sandoz argues that the WHO Meeting that Dr. West attended reflects knowledge of POSITAs concerning potential topical treatments containing azithromycin. (See dkt. entry no. 141, Sandoz's Supp'l Br. in Opp. to Pls.' Mot. in Limine No. 4.) The presentation, however, was not optimistic regarding the likelihood of success of such forms of treatment. (Trial Tr. at 455, 458, 498-99, 1343-45, 1065-66; DTX 216 at 16.) Additionally, experts on both sides agree that the treatment of trachoma is not relevant given that trachoma is a systemic disease. (Trial Tr. at 326, 492-93, 685, 1068, 1343-44.) For these reasons, the WHO references do not demonstrate a motivation to combine references or a reasonable expectation of success of such a topical ophthalmic treatment.

Sandoz has thus failed to prove by clear and convincing evidence that the '411 Patent is invalid for obviousness.

D. The ISV Patents [10]

1. The Prior Art

a. The Prior Art Relating to the '411 Patent

i. Zithromax®

Sandoz claims that what was known in 1996 in the art regarding Zithromax® -- an orally dosed, FDA-approved drug with azithromycin as the active ingredient -- is prior art for the ISV Patents. (Sandoz's Post-Trial Br. at 33.) See supra section II.C.1.d.iii for a discussion of Zithromax®.

ii. The '411 Patent Itself

Sandoz has claimed that the '411 Patent is prior art to the ISV Patents. (Sandoz's Post-Trial Br. at 33.) However, Dr. Reed admitted that he used December of 1996 as the cut-off date for prior art references asserted against the ISV Patents. (See Trial Tr. at 954-57.) Plaintiffs thus argued before trial that Dr. Reed's testimony prevented him -- and, by extension, Sandoz -- from relying on any prior art references issued after November of 1996, including the '411 Patent. The Court agreed, and entered an order precluding Sandoz from relying on art published after November of 1996 in establishing its prima facie case of obviousness. (See dkt. entry no. 137, 6-17-13 Order at 2 (stating, inter alia, that "Sandoz will be confined to its existing disclosures").)

[10] It is undisputed that the '113 Patent and '443 Patent are entitled to a priority date of March 31, 1998. (See DTX 2 at [63]; DTX 3 at [63]; Sandoz's Post-Trial Br. at 33 n.12.) It is also undisputed that the '893 Patent is entitled to a priority date of June 4, 2001. (See DTX 4 at [22] (noting that the '893 Application was filed on June 4, 2002); Sandoz's Post-Trial Br. at 8 n.9.) See also 35 U.S.C. § 102(b); New Railhead Mfg., 298 F.3d at 1293.

The Court nonetheless allowed Sandoz to elicit testimony from Dr. Reed about the alleged obviousness of the ISV Patents based, in part, on the '411 Patent. (See Trial Tr. at 794-808.) Plaintiffs objected to the introduction of such testimony, and the Court reserved decision on the objection. (See id. at 794-803.) Plaintiffs have raised their argument anew in their post-trial brief. (See Pls.' Post-Trial Br. at 38 n.23.)

The Court now reaffirms the decision expressed in the 6-17-13 Order: because Dr. Reed stated that his opinions were limited to art published in or before December of 1996, Sandoz is precluded from relying on art published after December of 1996 when attempting to prove that the ISV Patents are invalid under 35 U.S.C. § 103(a). The Court, however, anticipates the possibility of appeal. Thus, the Court has taken the precaution of considering the parties' arguments concerning the extent to which the '411 Patent renders claims asserted from the ISV Patents obvious.

The '411 Patent claims a method of topically treating ocular infections using the antibiotic azithromycin, but the patent does not indicate the specific amount of azithromycin. (Trial Tr. at 805-07; see also DTX 1 at cols. 5-6.) The '411 Patent lists eight different examples of formulations, some water-based and some ointment-based. (DTX 1 at col. 2, line 65 to col. 5, line 6.)[11] Dr. Ahmed expressed concerns regarding the stability of azithromycin in the water-based examples since azithromycin was known to be unstable in water, and Dr. Lee testified that other ordinary researchers would have similar concerns. (JTX 101 at 42-43, 52, 56; Trial Tr. at 1331-33, 1338-40.) The '411

[11] AzaSite®, the New Drug Application held by Inspire that is at issue here, is a water-based formulation. (Trial Tr. at 1301-02, 1425.)

Patent expresses a preference for ointment formulations over water-based formulations. (Trial Tr. at 1062, 1340.) There is no data or information in the '411 Patent regarding the stability of these water-based examples. (Id. at 1063, 1331-32, 1339-40.) The data and information showing the long-term stability of a topical azithromycin formulation is provided in the '893 Patent. (Id. at 1331-32, 1425-26; DTX 4, cols. 23-24 tbl. 12.)

Dr. Ahmed explained some of the examples in the '411 Patent at length. Dr. Lee and Dr. Reed also provided expert testimony to assist in understanding these examples.

Example 5 of the '411 Patent, which Dr. Ahmed believed would be suitable for treating ocular infections, contains polymeric agents -- specifically Carbopol 934P -- that impart viscosity to a formulation. (JTX 101 at 23, 42; DTX 1 at col. 3, lines 57-65; see also Trial Tr. at 869.) The reason viscosity is important to ophthalmic formulations is that the eye rapidly clears materials that are placed in it, and "viscosity provides the opportunity for the active [ingredient] to stay at the site of absorption for some period of time." (JTX 101 at 42.)

Carbopol 934P is sometimes called a carbomer or carbomer product; carbomers are aqueous-based. (Id. at 50; Trial Tr. at 756, 759-60.) Both Carbopol 934P and polycarbophil -- the polymer disclosed as the delivery vehicle in the ISV Patents (see, e.g., DTX 2 at col. 14, lines 56-57; DTX 4 at col. 27, lines 51-55) -- are polyacrylic acids. (Trial Tr. at 758; JTX 101 at 51.) What distinguishes polycarbophil from Carbopol 934P or carbomers is the unique nature of polycarbophil's crosslinking agent (i.e., linking of

polymer chains) and the density of the polymers. (Trial Tr. at 758, 880, 1338.)[12] According to Dr. Reed, because of this unique crosslinking agent, "[P]olycarbophil swells dramatically, but it never goes completely in to the solution," and it holds its formation. (Id. at 758-59; see also id. at 899-900 (polycarbophil is "water-swellable" and "water-insoluble").) Carbomers, on the other hand, are completely soluble (meaning they disperse completely into the solution) and do not have the "staying formation." (Id. at 758-59, 882.)

Sandoz's expert Dr. Reed testified that the '411 Patent's illustration of an ophthalmic gel formulation, prepared by putting azithromycin in a polyacrylic acid polymer, made "a lot of sense." (Id. at 866-67; see also DTX 1 at col. 2, lines 40-48.) Plaintiffs' expert Dr. Lee testified, however, that the '411 Patent's reference to Carbopol is not a reference to polycarbophil and that the '411 Patent's description and examples do not disclose the use of polycarbophil as a delivery vehicle. (Trial Tr. at 1333-34, 1337.)

Dr. Lee and Dr. Reed disagreed about whether the use of Carbopol 934P in example 5 would create a gel. In-situ gelling formulations come out of the container as a drop, but when the drop hits the eye, there is a big increase in viscosity, and the formulation then acts like a gel. (Id. at 755-56.) In-situ gelling "systems that increase in viscosity on application are based on polymers." (Id. at 755.) While Dr. Reed testified that he could not tell whether the addition of Carbopol 934P in example 5 would create

[12] The name "Carbopol" itself is a trademarked brand-name encompassing several polymers. (Trial Tr. at 759.) Both Dr. Lee and Dr. Reed note that there is a polyacrylic acid that was once referred to as Carbopol 976, but is now called Noveon® AA-1. This is polycarbophil and not a carbomer. (Id. at 781, 867, 879-80, 891-92, 895, 1335-37.)

an in-situ gelling system, Dr. Lee unequivocally testified that Carbopol 934P is not an in-situ gelling polymer. (Id. at 883, 886-87, 1334-35.)

According to Dr. Lee and Dr. Ahmed, water would be part of a formulation containing polycarbophil or Carbopol 934P; however, the use of water would create issues regarding the long-term stability of such a formulation when combined with azithromycin because of the degradation (or hydrolysis) of azithromycin and macrolides in water. (Id. at 1338-41, 1340; JTX 101 at 52, 56.) The '411 Patent, which lacked stability data, did not provide any mechanism that would alleviate these concerns. (Trial Tr. at 1340.) Dr. Lee also explained that a POSITA reviewing the '411 Patent would be concerned because it indicates that the inventor of the '411 Patent only made ointments, not the water-based formulations. (Id.) Dr. Lee and Dr. Reed both testified that the '411 Patent gives a preference for ointments over water-based formulations. (Id. at 1062, 1340.)

Dr. Ahmed added additional detail about the pH of the formulation in example 5. He testified that the natural pH of tears is 7.2, and for example 5, he considered 4 to 6 as the range for the formulation's pH, because that is the range of pH that is tolerated by the eye and does not cause massive irritation. (JTX 101 at 51-52.) Azithromycin's stability is also pH-dependent, and generally speaking, hydrolytic instability worsens as pH values increase. (Id. at 57-58.) Thus, a formulator would prefer to use azithromycin at a lower pH.

Dr. Reed and Dr. Ahmed also discussed the in-situ gelling formulation described in example 7 of the '411 Patent. That formulation is liquid at room temperature and is applied as a drop but gels when it hits the eye from the higher temperature of the eye. (Trial Tr. at 888; JTX 101 at 60-62.) Dr. Ahmed explained that the conversion is caused by Carbopol, which is a pH-triggered gelling system, and the formulation would gel at a pH near the tear pH, approximately 7. (JTX 101 at 61-62.)

Dr. Lee concluded that the examples used in the '411 Patent would not have motivated a POSITA to use polycarbophil in an azithromycin formulation. (Trial Tr. at 1338.) Dr. Reed concluded, in contrast, that, in 1996, example 5 illustrated that "it would be a good idea to add azithromycin with Carbopol," and he also explained that polycarbophil is another option for POSITAs to build an ophthalmic delivery vehicle. (Id. at 870, 889.) Dr. Reed also concluded that the '411 Patent, specifically example 7, taught "the idea of in situ gelling ophthalmic systems." (Id. at 887-88.)

b. Potential Vehicles for Topical Ophthalmic Formulations

The experts in the field agree that designing ophthalmic drug delivery systems is challenging and incredibly difficult. (See, e.g., DTX 84 at xv ("It is not an overstatement to say that designing drug delivery systems for the eye is an incredibly difficult task."); Trial Tr. at 540, 1298-1303.) "Various dosage forms and delivery systems applied topically into the eye include solutions, suspensions, semi-solids, and inserts." (DTX 84 at 31.)

i. Considerations

Dr. Reed and Dr. Lee both testified that a variety of factors must be considered when developing a topical ophthalmic formulation, including: (1) tonicity, (2) viscosity, (3) solvent type, (4) buffer type, (5) pH, (6) preservatives, (7) toxicity, (8) irritation/patient comfort, and (9) ocular penetration. (Trial Tr. at 958-60; see also Trial Tr. at 1298-1301.)

(a) Toxicity and Tonicity

The prior art relating to the tonicity and toxicity of delivery vehicles for topical formulations in the ISV Patents is the same as the prior art for the '411 Patent. Essentially, both tonicity and toxicity relate to the eye's reaction to external substances that enter the eye. (See supra section II.C.1.c.)

(b) Viscosity

Viscosity is important to ophthalmic formulations because the eye naturally clears foreign materials that enter it. The level of viscosity determines the opportunity of the active ingredient to remain at the absorption site for a period of time. (JTX 101 at 42.) One of the problems with using ointments for ocular infections is that they tend to have too high a viscosity, which allows the drug to stay at the site of application for longer but also causes discomfort to the patient. (Trial Tr. at 960-61.)

(c) Irritation

Dr. Reed testified that, with respect to irritation, a formulator would consider patient comfort and "would want to minimize the irritancy, burning, foreign body sensation, eyelid drag and similar inconvenience." (Id. at 960.) A POSITA would want a formulation to have

pH and tonicity levels that are close to that of the eye to reduce irritation to the eye. (Id.) While a high viscosity allows the active ingredient to remain at the site of application for a longer period of time, a POSITA would also be aware that patients find formulations with high viscosities to be inconvenient and uncomfortable. (Id. at 960-61.)

(d) Ocular Penetration

Dr. Reed admitted that ocular penetration was a factor in formulating topical ophthalmic treatments as well, because a POSITA would want the formulation to reach the site of infection, and infections can be below the cornea's surface. (Id. at 961-65.) Thus, the factors relating to a substance's ability to penetrate ocular tissue are relevant considerations not only for choosing the active ingredient but for choosing the delivery vehicle as well. (Id. at 965-67.) These factors include molecular weight, osmality, solubility/stability, pH/ionization, and the partition coefficient or log P. (Id. at 845-47, 965-67, 1019; see also supra section II.C.1.c, d.)

Antibiotics that may be effective when dosed non-topically (through injections or systemic administration) may not be effective when applied topically to treat ocular infections. (DTX 4 at col. 1, lines 29-60.) Not only must a topical ophthalmic formulation be able to penetrate ocular tissue, but also it must be able to impart an effective dose. (Id. at col. 1, lines 44-49.) Many drugs lack the requisite penetration ability with respect to ocular tissues. (Id. at col. 1, lines 48-49.) The external layers of the eye are distinct from tissues found in the intestinal tract or the stomach, and thus, drugs that are readily absorbed following

systemic administration may be incapable of sufficiently penetrating ocular tissue when applied topically. (Id. at col. 1, lines 49-57; see also Trial Tr. at 971-78.)

Dr. Reed further explained that a topical ophthalmic treatment should be in a solution because a suspension would have difficulty penetrating the cell membrane. (See Trial Tr. at 847-48.) The solubility of a formulation "is important because it determines the maximum concentration of [a] drug that can be formulated as a solution product." (Id. at 967.) According to Dr. Reed, "the higher the solubility, the higher the concentration. The higher the concentration, the more driving force you have." (Id. at 966.) It is possible to create ophthalmic medications in the form of suspensions, which can go into a solution when they enter ocular tissue; however, solutions are preferred to suspensions in terms of patient compliance. (Id. at 847-48, 967.)

The "[s]tability of the aqueous composition is a concern because a formulator would seek to minimize degradation" of active ingredients and other ingredients that "contribute to the performance of the product" (e.g., viscosity agents if a certain viscosity needs to be maintained). (Id. at 967-69.) Azithromycin, however, was known to be unstable and to undergo hydrolysis in water, meaning that it would decompose into an inactive substance. (Id. at 1304, 1421-25; Yu-Kyoung et al., Formulation and Efficacy of Liposome-Encapsulated Antibiotics for Therapy of Intercellular Mycobacterium Avium Infection, 39 ANTIMICROBIAL AGENTS & CHEMOTHERAPY 2104, 2107 (Jan. 1995) (hereinafter "PTX 33").)

(e) pH and Ionization

Dr. Reed explained that "PH is a measure of your proton concentration" or the "hydronium ion concentration or lack thereof." (Trial Tr. at 738.) The lowest possible pH is 1, and the highest is 14. (Id. at 739.) A pH of 7 is neutral. (Id. at 738-39.) A substance with a pH between 1 and 7 is acidic, with 1 being the most acidic, and a substance with a pH between 7 and 14 is basic, with 14 being the most basic. (Id. at 739-40.) A low pH indicates a large amount of available protons, which have a positive charge. (Id. at 738.) With a pH of 14, "you're not going to see any protons at all." (Id.)

Dr. Reed explained the relationship between pH and solubility. A pH of 1, which is the most acidic and the most highly charged, is the most soluble. (Id. at 740, 742.) Dr. Reed testified that an azithromycin formulation with a pH of 5 and below has lots of protons and "likes" to go into water. (Id. at 740.) Joining a proton to an azithromycin formulation increases the formulation's affinity for water. When the proton is gone and the charge is neutral, the formulation prefers to go into oil. (Id. at 738-39.)

Dr. Reed testified that a POSITA as of 1996 would believe that azithromycin was soluble at a pH of 5, but a POSITA would prefer a higher pH because if the formulation is "soluble at the higher pH, then it's more comfortable" to the eye. (Id. at 742-44.) The eye's pH is between 7 and 7.4. (Id. at 744.)

Dr. Reed explained that a formulator can control the pH of a substance by using a buffer that resists changes in pH. (Id. at 740-41.) A buffer can be used around the azithromycin formulation to maintain its lower pH, which may be necessary for

azithromycin's stability in water. Once in the eye, the tear could overcome the product's buffer. (Id. at 744.)

Dr. Reed also testified that topical drugs in their charged (or ionized) form have greater difficulty penetrating the lipid bilayer of ocular tissues than in their uncharged (non-ionized) form. (Id. at 1018-19.) At a pH of 7, 93% of azithromycin will be ionized, meaning that azithromycin is less soluble but is better able to penetrate ocular tissue. (Id. at 1019-20.) At a pH of 5, approximately 99.9% of azithromycin is ionized, meaning that azithromycin is more soluble (can easily go into a solution) but is less able to penetrate ocular tissue. (Id. at 1020-21.)

ii. Options

The parties disputed the scope of the options available as delivery vehicles for topical ophthalmic treatments using azithromycin. Dr. Lee testified that there were eight general types of delivery vehicles available: "solutions, gels, emulsions, combination systems, drug permeability enhancers, suspensions, oils, colloidal systems, [and] ocular inserts." (Id. at 1315-16; see also Chrystéle Le Bourlais et al., Ophthalmic Drug Delivery Systems – Recent Advances, 17 PROGRESS IN RETINAL & EYE RESEARCH 33, 33-58 (1998) (hereinafter "PTX 15"); Hitoshi Sasaki, Delivery of Drugs to the Eye by Topical Application, 15 PROGRESS IN RETINAL & EYE RESEARCH 583, 583-620 (1996) (hereinafter "PTX 16").) Within each type, there are several examples of options. (Trial Tr. at 1316-19.) The most significant of these general types are discussed below.

(a) Colloidal Systems

Dr. Lee testified that, if required to ignore azithromycin's instability in water, among the eight categories of options for delivery systems, he would have first selected colloidal systems as the delivery vehicle for an azithromycin formulation because, "this system would encase the molecule to . . . protect the molecule from degradation." (Id. at 1317-18.)

(b) Combination Systems

Dr. Lee testified that, if again forced to ignore the fact that azithromycin degrades in water, his second choice would be combination systems. (Id. at 1319.) Many examples in this category included combinations of colloidal carriers with gel systems. (Id.) These colloidal carrier-gel combinations were advantageous because the formulation had the benefit of the colloidal system protecting the molecule and the gel increasing viscosity to assist the drug in remaining in the location of application in the eye. (Id.)

(c) Solutions

"Most ophthalmic drugs are formulated as solutions." (Mark B. Abelson et al., How Topical Drugs Work, REVIEW OF OPHTHALMOLOGY 89 (Nov. 1995) (hereinafter "DTX 167").) A solution is a "molecular dispersion" in, most often, water. (Trial Tr. at 542.) Of the many options available for ophthalmic delivery vehicles, Dr. Reed believed the best option was a simple solution –– i.e., an eye drop –– which is water-based. (Id. at 750-51.) Dr. Reed explained that the major drawback of simple solutions is that they get "washed out of the eye very quickly," which is a concern because the length of time the drug stays in the eye directly affects the ability of the drug to penetrate ocular tissue. (Id. at 750-52.)

(d) Suspensions

"Some drugs are formulated as suspensions; the drug is finely divided up (but not dissolved) into a liquid." (DTX 167 at 89.) Suspensions can be helpful when the sustained release of the drug is essential to the treatment or when the agent is somewhat insoluble. (Id.)

(e) Ointments

Ointments fall under the category of oils. (Trial Tr. at 1316.) Ointments, which are petroleum based, offer greater residence time in the eye than simple solutions. (Id. at 752-53.) The problem with using ointments is that they are messy and impair vision. (Id. at 753-54; DTX 167 at 89.) Other disadvantages include imprecise dosing and foreign body sensation. (DTX 167 at 89.) Dr. Reed testified that a POSITA would not consider ointments to be an optimal vehicle for ophthalmic formulations. (Trial Tr. at 754.)

(f) Gels

Dr. Reed testified that around the time of the inventions at issue, there were relatively new delivery systems called in-situ gelling. (Id.) An in-situ gelling system would come out of the bottle as an eye drop, and, when the formulation came in contact with the eye, the gelling system would increase in viscosity and create a gel. (Id. at 523-24, 528, 755; DTX 167 at 89.) Gels could enhance penetration and prolong the drug's residence in the eye. (DTX 167 at 89.)

Dr. Lee explained that there are 40 examples of materials that could be used as gels, each with varying viscosities, molecular weights, and crosslinking agents. (Trial Tr. at 1319-21.) "[A] person of ordinary skill in the art would have to both pick one of these gels and

then, also, figure out the correct viscosity or molecular weight[.]" (Id. at 1320-21.) These gels can also be combined to create new delivery vehicles, thereby increasing the number of gel options. (Id. at 1321.) Dr. Lee opined that "[t]here's no reason to prefer one gel over the other." (Id.)

Dr. Lee further testified that if a gel system was the chosen delivery vehicle for an azithromycin formulation, "the formulation would not be stable." (Id.) However, Dr. Reed asserted that he would use a gelling system. He stated that he would select polycarbophil, a gel in the InSite trademarked product DuraSite®, as his first option, and he only briefly mentioned other gels such as Gelrite and Carbopols. (Id. at 755-56, 913, 951.)

Dr. Reed additionally mentioned that he had two patents for in-situ gelling systems. (Id. at 755.) While he was employed by Ciba Geigy, he patented an in-situ gelling system using chitosan, a soluble, natural polymer. (Id. at 527-28.) While he was employed by Alcon Labs, he developed a patented in-situ gelling system using a crosslinked polyacrylic acid (Carbopol). (Id. at 522-24.)

The record developed at trial described, in depth, a few of the gel-type products and inventions that pre-existed the ISV Patents at issue.

(i) DuraSite®

In testifying that a POSITA would choose polycarbophil as a delivery vehicle, Sandoz's expert Dr. Reed pointed to a 1995 article addressing DuraSite® written by Dr. Lyle Bowman (one of the inventors of the '893 Patent that is at issue in this case) and Rajesh Patel of InSite Vision. (Id. at 756-71 (citing Lyle Bowman & Rajesh Patel, Drug Release from

Gel-Forming Ophthalmic Suspensions, 22 PROC. INT'L SYMP. CONTROLLED RELEASE OF BIOACTIVE MATERIAL 157 (1995) (hereinafter "DTX 189").) The article is critical of current systems for topically administering ophthalmic drugs:

> Topical administration of ophthalmic drugs via conventional eye drops results in extensive drug loss, primarily due to spillage outside the eye and tear fluid dynamics which remove the solution rapidly through the nasolacrimal duct[1]. Typically, only a small fraction (1-3%) of an administered drug penetrates the cornea and reaches the intraocular tissues [2]. Thus, for drugs with short biological half-lives, frequent administration is necessary to maintain therapeutic levels of drug [sic] in the ocular tissues.
> . . . .
> [Suspensions, gels or ointments] offer certain improvements over conventional eye drops such as increased retention time leading to higher bioavailability, but have the disadvantages of being cosmetically unattractive, blurring vision for extended periods of time, and/or creating a foreign body sensation. Newer systems, such as inserts [6], collagen shields [7], and medicated contact lenses [8], have had limited success primarily due to lack of patient compliance. These systems are difficult for patients to administer, create a foreign body sensation and are easily displaced from the eye.

(DTX 189 at 157.)

The article explains that DuraSite, which easily can "be administered as a drop to the lower cul-de-sac of the eye," provides sustained drug release and extended contact with ocular tissues without causing foreign body sensation. (Id.) DuraSite is comprised of salts and polycarbophil, "a polyacrylic acid lightly crosslinked with divinyl glycol." (Id.; see also Trial Tr. at 757-61.)[13] Notably, Dr. Bowman explained in his deposition that the word "DuraSite" without the trademark symbol "could be a number of different polymer systems," including

[13] Dr. Reed testified that the presence of sodium chloride in DuraSite® was to adjust tonicity -- to ensure that the osmotic pressure was correct. (Trial Tr. at 863-64.)

Carbopol polymers, but that the polymer in the trademarked product DuraSite® is polycarbophil. (Lyle Bowman Dep. Tr. at 20-21, 64-65, 109-10 (hereinafter "JTX 102").)

The Bowman article describes DuraSite's high viscosity, which reduces the loss of medicine due to tearing or blinking and allows the drug to reside in the eye for a longer period of time. (DTX 189 at 157-58; see also Trial Tr. at 758.) Dr. Reed explained further that polycarbophil "likes mucin" (the mucous-type, inner layer of the tear film) and remains in the eye longer. (Trial Tr. at 763-64.)

The article concludes that "[v]arious soluble and insoluble drugs have been successfully formulated in the DuraSite system ranging from low molecular weight organic compounds to high molecular weight proteins." (DTX 189 at 158.) Dr. Reed testified that his understanding of the significance of this passage is that the DuraSite® "system could work with not just compounds that are soluble enough to hit the target concentration" but also with drugs that cannot attain the target concentration in a solution and instead require a suspension. (Trial Tr. at 764.) Dr. Reed further explained that while high molecular weight substances have difficulty penetrating the cornea, DuraSite® is a good vehicle even for such substances. (Id. at 767.)

Dr. Reed concluded that a POSITA in 1996 would understand from the article "that there was a likelihood of incorporating medicine into the DuraSite® delivery system which was comprised, in part at least, of polycarbophil." (Id. at 896.)

(ii) AquaSite®

Sandoz also asserts that the AquaSite® box label, a now discontinued dry-eye treatment, is prior art. (Sandoz's Post-Trial Br. at 33.) AquaSite® was an FDA-approved, over-the-counter lubricant in the form of an eye drop that contained DuraSite®. (Trial Tr. at 769-771, 861-62, 1047; AquaSite® Box Label (hereinafter "DTX 50").)[14] The box states that DuraSite® and AquaSite® are registered trademarks of InSite Vision. (DTX 50.)

The AquaSite® label indicates that it contains the trademarked DuraSite®, and lists the ingredients of DuraSite®, which include polycarbophil. (Id.; see also Trial Tr. at 770-71; JTX 102 at 64-65, 70-71.) Dr. Reed testified that a POSITA, in the mid-1990s, would have been aware of AquaSite®, that it contained DuraSite®, and that it gelled upon instillation. (Trial Tr. at 776, 862, 912.) While Dr. Reed knew the amount of polycarbophil in AquaSite® because he had access to confidential information related to this litigation, Dr. Lee testified and Dr. Reed confirmed that the AquaSite® label lacks information regarding the quantities of polycarbophil and other ingredients in the formulation. (Id. at 1047-51, 1312, 1321-22.) Moreover, AquaSite® lacked an active ingredient, and the label provides no information regarding its efficacy, stability or safety with any active ingredient. (Id. at 1047, 1051, 1322-24.)

(iii) The 1993 InSite Patent

In attempting to establish obviousness, Sandoz also relies on a 1993 patent owned by InSite entitled "Ophthalmic Suspensions." (Sandoz's Post-Trial Br. at 33; U.S. Patent No.

[14] DuraSite® itself does not require FDA approval because it is intended to be used in products that in their entirety are subject to FDA approval. (Trial Tr. at 769-70.)

5,192,535 at [22], [54], [73] (filed June 27, 1990) (hereinafter "the '535 Patent" or "DTX 82").) The '535 Patent covers an in-situ forming gel system for delivering an antibiotic to the eye with the use of polycarbophil. Dr. Reed described this patent as a delivery system containing "polyacrylic acid, lightly crosslinked, formulated so that at low pH it's in a droppable form, that is from an ophthalmic bottle, it comes out as a drop." (Trial Tr. at 777.) When the delivery system comes out of the bottle and hits the eye, it gels and becomes thick, which resists removal from the eye. (Id.)

The '535 Patent gives examples of ophthalmic delivery systems that use polycarbophil as well as other polyacrylic acids. (DTX 82 at cols. 10-13; Trial Tr. at 779-91, 1057-58.) Dr. Reed testified that he believed that the patent describes, in part, the DuraSite® product. (Trial Tr. at 794.)

The '535 Patent also includes an illustrative but non-exclusive list of medicaments that could be incorporated into the topical delivery system. (DTX 82 at col. 8, line 61 to col. 9, line 27.) As a result, Dr. Reed testified that this was a very flexible delivery system. (Trial Tr. at 784-86, 865.) Erythromycin was specifically listed as a potential medicament. (Id. at 784-85; DTX 82 at col. 9, line 14.) Dr. Reed admitted on cross-examination, however, that the examples in the '535 Patent only referenced using fluorometholone and pilocarpine as the active ingredients, and no examples used erythromycin. (Trial Tr. at 1058-59.) Dr. Reed further acknowledged that, to his knowledge, "there is no commercial product containing erythromycin and polycarbophil or any other polymer that's disclosed in the '535 patent." (Id. at 1060.)

As part of its topical ophthalmic delivery system, the '535 Patent specifically claims in claim 1, "an aqueous suspension at a pH of from about 3 to about 6.5 and an osmotic pressure of from about 10 to about 400 mOsM". (DTX 82 at col. 13, lines 41-43.) Dr. Reed explained that a formulator would not want a pH as high as 7 because the formulation needs room to increase in viscosity, and at a pH of 7, the formulation would essentially just be administered as a gel. (Trial Tr. at 786.) It is therefore best to keep the pH down between 3 and 6.5. (Id.) With respect to the osmotic pressure range, Dr. Reed testified that, while the delivery system described in the '535 Patent is not dependent on osmolality, too low an osmolality can cause cells to blow up, and too high can cause cells to shrink. (Id. at 788-89.)

The '535 Patent also lists the percentage range of the crosslinked polymer particles for the inventions as .1% to 6.5% by weight based on the total weight of the suspension. (DTX 82 at col. 7, lines 42-44; Trial Tr. at 1056-57.) Dr. Reed testified that a POSITA could experiment with concentrations of the crosslinking agent within that range to obtain the desired viscosity such that the formulation still comes out as a drop. (Trial Tr. at 1057.) However, Dr. Reed acknowledged when questioned that there is a "65-fold difference between the low and high end of the concentrations of a polymer." (Id.)

Claim 1 of the '535 Patent also teaches the range of viscosity that a formulator could use for a formulation administrable in drop form; that viscosity is "from about 1,000 to about 30,000 centipoises". (DTX 82 at col. 13, lines 52-55.) Dr. Reed testified that this broad range indicates to a formulator that there is a lot of flexibility with this product, but it must be

administrable in drop form to the eye. (Trial Tr. at 791-92.) The higher the viscosity, the more thread-like (or gel-like) the formulation will be as it comes out of the bottle. (Id. at 792.)

(iv) Other Gel Options

Gelrite is an in-situ gelling system developed by Merck that was available in 1996. (Id. at 755-56, 913.) Dr. Reed testified that a POSITA in 1996 could have considered Gelrite as a delivery vehicle but that it was owned by Merck. (Id. at 913.) Merck used Gelrite for its marketed product, Timoptic-XE. (Id. at 755, 913.) Additionally, Dr. Reed described two of his own patents for in-situ gelling systems. (Id. at 522-24, 527-28.)

c. The WHO Report

Under normal circumstances, when a drug is administered with an aqueous eye drop, 90% of a dose of the active ingredient is lost 15 to 30 seconds after application. (DTX 216 at 16.) The WHO Report references delivery vehicles that allow the formulation to be administered as a drop and that slow the release of the active ingredient over an extended period of time. (Id. at 16-17.) The WHO Report lists several examples of gel and eye-drop systems, including DuraSite, Gelrite, and ion exchange resin. (Id. at 17.) Dr. Reed testified that he relied on this WHO Report in developing his opinions. (Trial Tr. at 932-38.)

As discussed supra section II.C.1.g, the Court finds that Sandoz failed to demonstrate that the WHO Report was published, and, therefore, the Court will not treat the Report as prior art. Moreover, even if the WHO Report were published, the Court would not find it significant that the Report cites to DuraSite as a method of topical drug delivery to the eye. (See DTX 216 at 17.) DuraSite® itself is simply a trade name, and the non-trademarked

word "DuraSite" could refer to a variety of polymer systems, including Carbopol polymers. (See JTX 102 at 20-21, 63-65.) There is no indication that Dr. Dawson, the presenter on topical azithromycin treatment for trachoma at the WHO Meeting, equated "DuraSite" with polycarbophil.[15] Thus, the reference in the WHO Report to "DuraSite" without the trademark indication is no stronger a reference to polycarbophil than the word "Carbopol" in the '411 Patent.

d. The ISV Patents

i. The '113 Patent

Claim 6 through claim 9 of the '113 Patent are at issue in this case, and those claims are dependent on claim 1 through claim 3. (See 5-23-13 Final Pretrial Order at 26; 7-31-12 Stip. & Order at 1.) Those claims are:

> **1.** A process for treating an eye, which comprises: topically applying an aqueous polymeric suspension of an azalide antibiotic, wherein said suspension comprises water, 0.01% to 1.0% of an azalide antibiotic, and 0.1 to 10% of a polymeric suspending agent.
>
> **2.** The process according to claim **1**, wherein said polymeric suspending agent is a water-swellable water-insoluble crosslinked carboxy-vinyl polymer.
>
> **3.** The process according to claim **2**, wherein the polymer comprises at least 90% acrylic acid monomers and 0.1% to 5% crosslinking agent.

(DTX 2 at col. 14, lines 37-47.)

[15] Dr. Dawson was a colleague of Dr. Bowman, and the two had discussed formulating topical compositions containing azithromycin. (JTX 102 at 23-25, 76-77.) And Dr. Bowman testified that the word "DuraSite" (in the absence of the trademark) was a general term used by InSite for a polymer delivery system, which included polycarbophil and other polymers like Carbopol. (Id. at 20-21, 64-65, 109-10.)

6. The process according to claim **3**, wherein said polymer comprises a polycarbophil.

7. The process according to claim **3**, wherein said polymeric suspending agent is contained in an amount of from about 0.5 to 1.2%.

8. The process according to claim **7**, wherein said polymer has a monodisperse particle size distribution.

9. The process according to claim **8**, wherein said azalide antibiotic comprises azithromycin.

(Id. at col. 14, lines 55-63.)

ii. The '443 Patent

The claims at issue from the '443 Patent are claim 16 and claim 44. (See 5-23-13 Final Pretrial Order at 26; 7-31-12 Stip. & Order at 1.) These claims state:

16. A topical ophthalmic composition comprising an aqueous polymeric suspension comprising water, 0.01% to 1.0% of an azalide antibiotic and 0.1 to 10% of a polymeric suspending agent, wherein said topical ophthalmic composition has an osmotic pressure of from 10 to 400 mOsM and wherein said composition does not contain constituents that are physiologically or ophthalmically harmful to the eye.

(DTX 3 at col. 16, lines 14-20.)

44. A topical ophthalmic composition comprising an aqueous polymeric suspension comprising water, from about 0.1 to about 5.0% of an azalide antibiotic, and 0.1 to 10% of a polymeric suspending agent, wherein said topical ophthalmic composition has an osmotic pressure of from 10 to 400 mOsM and wherein said composition does not contain constituents that are physiologically or ophthalmically harmful to the eye and said topical ophthalmic composition is in the form of a depot which is capable of sustained release of said azalide antibiotic.

(Id. at col. 17, lines 45-54.)

iii. The '893 Patent

Claims 4, 6, 7, 9-12, 30, 36 and 40 of the '893 Patent are at issue in this case. (See 5-23-13 Final Pretrial Order at 26; 7-31-12 Stip. & Order at 1.) These claims are dependent on claims 1-3, 5, 23, and 29. These claims state:

> **1**. A composition comprising water, a polymeric suspending agent and an azalide antibiotic, wherein said composition has a pH of about 6.0 to 6.6.
>
> **2**. The composition of claim **1**, wherein said composition is an ophthalmic composition.
>
> **3**. The composition of claim **2**, wherein said polymeric suspending agent is a water-swellable water-insoluble crosslinked carboxy-vinyl polymer.
>
> **4**. The composition of claim **3**, wherein said polymer comprises at least 90% acrylic acid monomers and about 0.1% to about 5% of a difunctional crosslinking agent, wherein said polymeric suspending agent is contained in an amount of about 0.5% to about 1.2%.
>
> **5**. The composition of claim **1**, wherein said composition is incorporated into a formulation administrable in a depot format.
>
> **6**. The composition of claim **5**, wherein said depot contains sufficient azalide antibiotic to maintain the azalide antibiotic above the MIC_{50} for at least about 12 hours after administration.
>
> **7**. The composition of claim **1**, wherein said azalide antibiotic is azithromycin.

(DTX 4 at col. 27, lines 42-65.)

> **9**. The composition of claim **1**, wherein said azalide antibiotic is present at a concentration of about 0.1% to about 10.0%.

10. The composition of claim **1**, wherein said composition has a pH of about 6.0 to about 6.5.

11. The composition of claim **1**, wherein said composition has a pH of about 6.2 to about 6.4.

12. The composition of claim **1**, wherein said composition has a pH of about 6.3.

(Id. at col. 28, lines 45-53.)

23. A method of treating a patient infected with a bacterial infection comprising administering a composition comprising an azalide antibiotic formulation and a polymeric suspending agent to a subject in need thereof in an antibacterial effective amount, wherein said composition has a pH from about 6.0 to about 6.6.

(Id. at col. 29, lines 50-55.)

29. The method of [claim] **23**, wherein said composition is topically applied to the eye.

30. The method of claim **29**, wherein said polymeric suspending agent is a water-swellable water-insoluble crosslinked carboxy-vinyl polymer, and wherein said carboxy-vinyl polymer comprises at least 90% acrylic acid monomers and about 0.1% to about 5% crosslinking agent and a difunctional crosslinking agent.

(Id. at col. 30, lines 1-8.)

36. The composition of claim **2**, wherein said polymer comprises at least 90% acrylic acid monomers and about 0.1% to about 5.0% of a difunctional crosslinking agent, wherein said polymeric suspending agent is contained in an amount of about 0.5% to about 1.2%.

(Id. at col. 30, lines 40-44.)

And, finally:

> **40.** The method of treating a patient of claim **23**, wherein said administering is one or two doses of said composition per day for at least six days.

(Id. at col. 30, lines 62-64.)

e. Motivation to Combine References for ISV Patents

Sandoz relied on Dr. Reed's testimony in an effort to demonstrate a motivation to combine references for the ISV Patents. Dr. Reed testified that as of 1996, POSITAs were aware of in-situ gelling delivery systems that increased the efficacy of an antibiotic by prolonging contact time. (Trial Tr. at 754; DTX 167 at 89.) According to Dr. Reed, Dr. Ahmed taught in the '411 Patent that azithromycin could be used with such an agent. (Trial Tr. at 866-67.) A POSITA in 1996 would have been aware of DuraSite®, and InSite's own '535 Patent described the DuraSite® product and the concept of an in-situ forming gel system using polycarbophil (also known as Carbopol 976) as the polymer to deliver ophthalmic drugs to ocular tissue. (Id. at 755-63, 776, 779-82, 794, 858-61, 890.) Dr. Reed testified that polycarbophil had been around since approximately 1991. (Id. at 861.) AquaSite®, which contained polycarbophil, was a commercially available product in the mid-1990s. (Id. at 861-62.)

i. The '535 Patent

Dr. Reed's assertions that the ISV Patents were obvious were heavily based on his opinion that the '535 Patent disclosed a great deal of information regarding in-situ gelling

delivery systems using polycarbophil. Specifically, Dr. Reed testified that the '535 Patent encompassed:

- the '113 Patent's:
    - listed percentages of the polymer, the crosslinking agent, and the polymeric suspending agent (specifically polycarbophil) (id. at 789-90, 898-907; DTX 82 at col. 2, lines 34-42, col. 5, lines 44-49, col. 7, lines 42-46) [16];
    - reference to "monodisperse particle size distribution," which was related to the concept of uniform packing in the '535 Patent -- the idea that there is improved viscosity and increased residence of the treatment in the eye when there is uniform particle size (Trial Tr. at 907-08; DTX 82 at col. 7, lines 25-41);
- the '443 Patent's:
    - description of the osmotic pressure range of the topical ophthalmic composition (Trial Tr. at 914-15; DTX 82 at col. 7, lines 61-65);
    - idea of avoiding substances in ophthalmic formulations that will hurt the eye, which would also be common sense to a formulator (Trial Tr. at 915-16; DTX 82 at col. 3, lines 47-49, col. 7, lines 47-49, col. 7, lines 61-66);
    - idea of a depot for sustained release, which was one of the properties of the DuraSite® product (Trial Tr. at 916-18);
- the '893 Patent's:
    - description of the use of polycarbophil, the percentages of the polymeric suspending agent, and the method of sustained release of the antibiotic to ensure sufficient quantities over an adequate period of time (id. at 921-24);

[16] Dr. Reed testified that a POSITA would know, when faced with the disclosed range of the polymeric suspending agent in the formulation, to change the concentrations to get the desired viscosity that permits the formulation to come out as a drop. (Trial Tr. at 898-99, 1057.)

- listing of pH levels, although the pH range in the '893 Patent was on the high end of the pH range taught by the '535 Patent, which was 3 to 6.5 (Id. at 786-87, 926-27; compare DTX 4 at col. 28, lines 48-53, with DTX 82 at col. 7, lines 51-52);

- description of the polymer structure and the azalide antibiotic's dosing regimen (of one to two times per day for six days), which was the result of the sustained release of the antibiotic as taught in the '535 Patent (see Trial Tr. at 930-32).

Dr. Reed's testimony about the obviousness of the ISV Patents from the '535 Patent was disputed. Other evidence in the record demonstrated that the '535 Patent was extremely general. (Id. at 1326.) The '535 Patent's reference to crosslinked acrylic acid polymer systems was not limited to polycarbophil but included other polymers as well. (Id. at 1058, 1326.) Moreover, the description of the ranges of the possible properties of the polymer in the '535 Patent were quite expansive: a 16-fold range for molecular weight; a 65-fold range for concentration; a 30-fold range for viscosities; and a 30-fold range for particle size. (Id. at 1054-57; DTX 82 at col. 6, lines 28-39, col. 7, lines 42-44, col 13, lines 9-21.) The '535 Patent also discloses a 2000-fold range between the active ingredient's high and low concentrations. (Trial Tr. at 1057-58; DTX 82 at col. 13, lines 25-29.) Many combinations were possible within these ranges, and a researcher would need to figure out the proper figure within the ranges and the proper balance of these properties. (Trial Tr. at 1055-58.)

The '535 Patent discloses a laundry list of active ingredients that could be formulated into its polymer system, and nothing in the '535 Patent points a formulator in the direction of azithromycin as the drug of choice. (Id. at 1328-29; DTX 82 at col. 8, line 61 to col. 9, line 27.) Dr. Lee explained that a researcher would ordinarily focus on a patent's examples, but

the examples in the '535 Patent use only two active ingredients: fluorometholone and pilocarpine. (Trial Tr. at 1327-28; see also DTX 82 at cols. 10-13.) Erythromycin is on the '535 Patent's list of possible compounds, but no example uses erythromycin. (Trial Tr. at 1060, 1328-29; DTX 82 at col. 9, line 14) Dr. Reed conceded that erythromycin has never been formulated with any of the water-based polymer systems described in the '535 Patent, including polycarbophil. (Trial Tr. at 1060.) And according to Dr. Reed, azithromycin was known to have antibiotic properties at the time the '535 Patent was filed, yet the '535 Patent does not list it as a possible choice in the laundry list of compounds. (Id. at 1060-61.) Moreover, the '535 Patent lacks data regarding the stability in water of any of the compounds, let alone azithromycin, and azithromycin was known to be unstable in water. (Id. at 1303-04; see also DTX 82.)

ii. Other Considerations

In attempting to demonstrate a motivation to combine references, Sandoz also relies on Dr. Reed's testimony to the effect that some of the features of the ISV Patents were obvious for common-sense type reasons. For example, Dr. Reed testified that the percentage range of the azalide antibiotic listed in the '113 Patent (.01 to 1 percent) would have been obvious to a POSITA in 1996 because it was the common, typical range for the dosing of similar antibiotics. (Trial Tr. at 897; see also DTX 2 at col. 14, lines 38-42.) Likewise, Dr. Reed explained the pH level ranges in the '893 Patent would have been obvious to a POSITA in 1996 given what was known about the relationship between pH and viscosity. (Trial Tr. at 926-27.) Dr. Reed asserted that the '893 Patent's pH range of 6.0 to 6.5 in claim 10 was

obvious because a pH lower than 7 was necessary for the gelling to occur in the eye. (Id. at 926.)

As to claim 6 of the '893 Patent, which claims a formulation that is administrable in a depot containing "sufficient azalide antibiotic to maintain the azalide antibiotic above MIC_{50}" -- meaning a minimum inhibitory concentration that affects at least 50% of the bacteria -- for a minimum of 12 hours after administration (DTX 4 at col. 27, lines 60-63), Sandoz relies on DTX 183 (or "the O'Day article"), a 1994 study detailing the results of orally administered azithromycin in rabbits. (Sandoz's Post-Trial Br. at 40-41.) This study demonstrated that oral administration of azithromycin yielded concentrations of azithromycin greater than MIC_{50} for 24 hours after administration -- 12 hours longer than the 12 hours required by claim 6. (See DTX 183 at 635-39.) While the study dealt solely with the oral administration of azithromycin (on rabbits), Dr. Goren and Dr. Reed testified that a POSITA would expect topical administration of a drug in general to yield greater concentrations than oral administration. (See Trial Tr. at 231, 939-40, 990-97.)

Dr. Reed concluded that a POSITA in 1996 would have been motivated to attempt to use azithromycin in an in-situ gelling formulation because azithromycin was known to have a wide spectrum of activity and to "love tissue," and in-situ gelling systems were known to increase a drug's residence time in the eye. (Id. at 857, 908-10.) The use of polycarbophil in DuraSite® was already known, and the ISV Patents essentially involved "taking an antibiotic and putting it a known vehicle." (Id. at 856-57.)

iii. Azithromycin's Stability and Solubility in Water

Despite Dr. Reed's testimony of obviousness, there was also substantial evidence in the record that azithromycin's properties taught away from its use in a water-based delivery system. Dr. Reed conceded that the stability and solubility of azithromycin would have been a concern in formulating azithromycin in DuraSite®. (Id. at 969-70.) According to Dr. Lee's testimony and the prior art, azithromycin is known to be unstable in water and to decompose. (Id. at 1304, 1421-25; PTX 33 at 2107.) Dr. Lee and Dr. Bowman testified that Pfizer failed to develop a water-based azithromycin formulation and instead made a lyophilized (or "freeze-dried") formulation and that this failure further demonstrated the knowledge in the art that azithromycin is unstable in water. (Trial Tr. at 1305-07; JTX 102 at 185-86.)

Dr. Lee further testified that a researcher would have been discouraged from using an aqueous system with azithromycin for fear that azithromycin would be unable to dissolve. (Trial Tr. at 1272-73.) Dr. Reed conceded the same and explained that azithromycin is only completely soluble at a pH of 5 -- 100-fold different from water's pH of 7. (Id. at 742.)

While Dr. Reed relies on AquaSite® and its use of DuraSite® as key prior art references demonstrating a motivation to combine references, Dr. Lee aptly noted (and Dr. Reed conceded) that the AquaSite® box does not contain any information regarding the exact quantities of polycarbophil and other ingredients in the formulation. (Id. at 1047-51, 1312, 1321-22.) Moreover, AquaSite® does not have an active ingredient, and its label lacks information regarding its safety, stability, or effectiveness with any active ingredient, let alone a medicament like azithromycin known to be unstable in water. (Id. at 1047-51, 1322-24.)

Dr. Lee stated that, without this type of information, a formulator would "have no way to judge whether or not that's going to be [an] appropriate" vehicle for azithromycin. (Id. at 1321-22.) Dr. Lee also testified that the fact that AquaSite® uses water would pose a "serious concern" about using it with azithromycin, which is unstable in water. (Id. at 1323, 1325.)

Dr. Lee similarly testified that Dr. Reed's reliance on the 1995 Bowman article describing DuraSite® (DTX 189) was flawed, because, as Dr. Reed acknowledged, it lacked the information necessary to assess its compatibility with azithromycin, including the existence of any active ingredients, the polymer quantities, and safety and stability data. (Trial Tr. at 1047-54, 1324-26.) The article even recognized that the polycarbophil vehicle's success with a drug depended on the characteristics of the drug: "The mechanism of drug release from this system is controlled by diffusion, dissolution, erosion, or combinations of these mechanisms depending on the physico-chemical parameters of the drug." (DTX 189 at 158.) Additionally, prior to the ISV Patents, no commercial product with an active ingredient had been made with the polycarbophil vehicle described in the article. (Trial Tr. at 1047, 1054; see also JTX 102 at 68-69.)

iv. Polycarbophil Versus Other Delivery Vehicles

Even if the art did not teach away from aqueous vehicles for azithromycin, the art did not teach in favor of one formulation (like polycarbophil) over the plethora of other options. (Trial Tr. at 1315-21; see also PTX 15; PTX 16; PTX 123 at col. 14, lines 10-14; DTX 84 at 387-89, 428-30.) Dr. Reed's analysis -- which led to his conclusion that the art taught toward the use of polycarbophil -- is based on hindsight. Dr. Reed admitted on cross-examination

that in formulating his opinions on the obviousness of the ISV Patents, he focused on the prior art for DuraSite® and AquaSite®, because he knew DuraSite® contained polycarbophil, the delivery system at issue for the ISV Patents. (Trial Tr. at 951-53.)

Polycarbophil is a gelling option. Dr. Lee testified that, given azithromycin's known instability in water, a POSITA would likely have selected colloidal systems first out of the possible delivery systems, followed by combination systems. (Id. at 1317-20.) There are a number of options that fall under each of these categories. (Id. at 1316-19; see also PTX 15; PTX 16; DTX 84 at 428-30.) Dr. Lee further testified that if azithromycin's instability were ignored and if a POSITA looked past colloidal and combination systems to gel systems, there were about 40 different gel options, each with varying viscosities and molecular weights. (Trial Tr. at 1319-21; see also PTX 15 at 36-43; PTX 16 at 602-06; DTX 84 at 387-89, 417-21.) Moreover, a formulator could combine some of the gelling options to create even more options. (Trial Tr. at 1320-21.) According to Dr. Lee, there was no reason to select one gelling system over another. (Id. at 1321.) Despite the variety of options for gelling and non-gelling systems, Dr. Reed focused only on polycarbophil. (See id. at 755-56, 913, 951.) This hindsight analysis is improper.

f. Reasonable Expectation of Success for ISV Patents

i. Azithromycin and Polycarbophil

Dr. Reed testified that a POSITA in 1996 would have had a reasonable expectation of success of formulating a topical ophthalmic in-situ gelling system using azithromycin. According to Dr. Reed, the Bowman article (DTX 189) and the '535 Patent (DTX 82) taught

that polycarbophil, the primary ingredient in DuraSite®, was known to slow down the release of the antibiotic. (DTX 82 at col. 4, lines 17-23; DTX 189.) Azithromycin was known to remain in the tissue for long periods of time because of its affinity for tissue. (Trial Tr. at 910-11, 917-20.) Thus, Dr. Reed explained that a POSITA would have expected that the formulations described in the ISV Patents would be successful in attaining the sustained release of azithromycin to an eye. (Id. at 910-11.) The Bowman article taught that a variety of soluble and insoluble drugs at various molecular weights could be formulated successfully into the DuraSite® delivery vehicle. (DTX 189 at 158; Trial Tr. at 896.) Additionally, Dr. Reed testified that a POSITA would have known, and would have found it significant, that the DuraSite® delivery system was safe, effective, and had been used in AquaSite®, an FDA-approved, marketed product. (Trial Tr. at 768-70; see also DTX 189 at 158.)

Dr. Lee refuted Dr. Reed's testimony that a researcher would have had a reasonable expectation of success with a water-based delivery system for a topical azithromycin formulation. As discussed with regard to motivation to combine references for the ISV Patents, azithromycin was known to be unstable in water, and thus, a researcher would be discouraged from combining azithromycin with an aqueous delivery system. (See supra section II.D.1.e; see also Pls.' Post-Trial Br. at 41-42.) Moreover, Dr. Reed did not refute Dr. Lee's testimony that other options for delivery systems were available, such as colloidal and combination systems, and a POSITA would not have had a reasonable expectation of success using an aqueous delivery system containing polycarbophil over the other potential options. (See supra section II.D.1.e; see also Pls.' Post-Trial Br. at 41-42.)

Dr. Reed and Dr. Lee also both testified that finding a successful formulation requires the balancing of several factors -- e.g., efficacy, dosing, comfort, stability, and solubility -- and the correct balance can only be determined through trial and error. (See Trial Tr. at 958, 1298-1301.) Thus, a POSITA could not expect any particular formulation to be successful without experimentation in these circumstances.

ii. Concentrations

Dr. Reed testified that azithromycin was known to be successful in treating ocular infections when administered orally, which would indicate to a POSITA that applying it topically to the site of the infection, particularly using a gelling vehicle, would have a high chance of success. (Id. at 910-11, 929.) As for attaining adequate concentration levels, the O'Day article revealed azithromycin concentrations in rabbits that exceeded MIC_{50} levels at 24 hours after oral administration. (See DTX 183 at 635-39.) Sandoz argues that, based on this and because greater concentrations of a drug would be expected to be achieved from topical as opposed to oral administration, a POSITA would have had a reasonable expectation of "success in topically applying sufficiently high concentrations of azithromycin to an eye using a depot for sustained release . . . such that azithromycin levels would have remained above MIC_{50} levels for at least 12 hours." (Sandoz's Post-Trial Br. at 41-42.) Sandoz asserts that the requirement in claim 6 of the '893 Patent of concentrations above MIC_{50} for 12 hours is inherent with topical azithromycin. (Id. at 42.)

Dr. Lee, in contrast, stated that a researcher would not have had a reasonable expectation of achieving azithromycin concentrations of MIC_{50} for 12 hours after topical

application, because the prior art did not suggest that combining polycarbophil and azithromycin would have such an effect. (Trial Tr. at 1288-89, 1314-15.) Dr. Lee also explained that Dr. Reed's reliance on studies of the effects of oral dosing of azithromycin were misplaced because those studies could not predict penetration of topical dosing of azithromycin given the differences between the eye and the stomach. (Id. at 1315.)

iii. pH Levels

Claim 12 of the '893 Patent sets the pH of the formulation at 6.3. (DTX 4 at col. 28, lines 52-53.) The pH of a formulation affects many components of that formulation, including polymer effectiveness, comfort, stability, and solubility, and each factor cannot be addressed individually. (Trial Tr. at 744, 1307-09, 1312.)

Samir Roy, one of the inventors of the '893 Patent, testified that, in order to determine the pH of a composition, formulators would routinely experiment with pHs between 5 and 7. (JTX 103, Samir Roy Dep. Tr. at 56-57.) Dr. Reed and Dr. Lee both testified that such pH stability testing through experimentation was common amongst POSITAs. (See Trial Tr. at 740-44, 748, 1392-93.) A pH of 7.4 is the most suitable for comfort, but azithromycin is most soluble at a pH of 5.0, and only sparingly soluble at a pH of 7.0. (Id. at 742, 1013-14, 1308-09.) According to Dr. Lee, nothing in the art suggested that azithromycin would be stable, comfortable, or effective at a pH of 6.3. (Id. at 1308-10.)

iv. Dr. Reed's Own Experience

At the time the ISV Patents were filed, Dr. Reed had at least 10 years of experience developing topical ophthalmic formulations. (Id. at 515, 1073.) While working for Ciba

Vision, Dr. Reed acquired non-public information from InSite regarding polycarbophil and AquaSite®. (Id. at 1074-75.) Despite this, he never created -- or even suggested or attempted to formulate -- a topical ophthalmic azithromycin treatment with polycarbophil. (Id. at 1075.) These facts undermine Dr. Reed's assertion that the claimed inventions were obvious.

g. Secondary Considerations

i. Unexpected Results

Dr. Reed testified that it was not surprising to find higher levels of azithromycin in ocular tissues when polycarbophil was used than when it was not used. He testified that DuraSite®, which used polycarbophil, was known to work effectively and to retain concentrations of the active ingredient in the eye for a longer period of time. (Id. at 940-41.)

Several other experts, in contrast, opined that the claims of the ISV Patents are remarkable and unexpected. Dr. Lee explained that azithromycin administered once a day as a drop "is not supposed to work," but somehow it was successful. (Id. at 1350-51.) Moreover, azithromycin is known to be unstable in water and insoluble, yet these patents put it in a water environment, and it overcame these barriers. (Id. at 1351.)

Dr. Abelson and Dr. Ahmed testified that the topical application of azithromycin formulated with polycarbophil yielded unexpectedly high concentrations of the drug in ocular tissue, and these concentrations were higher than those seen with oral dosing. (Id. at 647-48, 1176-77, 1180; see also JTX 101 at 103.) Test results revealed a 60-fold increase in the concentration of azithromycin when dosed topically as opposed to orally. (Trial Tr. at 1172-

73, 1175-76; Declaration of Imran Ahmed in Supp. of '411 Patent Application (hereinafter "PTX 125").)

Dr. Abelson also testified that AzaSite®, the FDA-approved NDA at issue containing polycarbophil and azithromycin, had enhanced activity against bacteria that was believed to be resistant to azithromycin. (Trial Tr. at 1187-89; Mitchell H. Friedlaender & Eugene Protzko, Clinical development of 1% azithromycin in DuraSite®, a topical azalide anti-infective for ocular surface therapy, 1 J. CLINICAL OPHTHALMOLOGY 3 (1997) (hereinafter "PTX 118").) Dr. Abelson explained that this result was remarkable, and researchers do not know how azithromycin's effect is enhanced when formulated with polycarbophil. (Trial Tr. at 1189.)

ii. Long-Felt Need

Dr. Abelson testified that, prior to the inventions in the patents at issue, there was a long-felt, yet unmet need for an ophthalmic treatment for ocular infections that could be dosed topically once daily. (Id. at 670.)

Prior to the inventions at issue, topical ophthalmic treatments required multiple doses per day for extended periods of time. (Id. at 664-69; PTX 12 at 26.) The frequent dosing schedule led to patient-compliance issues, which resulted in the development of organisms resistant to treatment and incomplete treatment of the ocular infection. (Trial Tr. at 488, 668-70, 768, 1299.) While Dr. Goren testified that patient compliance was not an issue, his testimony was contradicted by every other expert witness at trial, including Dr. West, Dr. Reed, Dr. Lee, and Dr. Asbell. (Id. at 247, 488, 668-70, 768, 1299.)

AzaSite® satisfied the long-felt need for reduced dosing regimens for topical treatments and became the first and only FDA-approved, topical ophthalmic treatment with once-daily dosing. (Id.) AzaSite® has only been approved by the FDA for the treatment of conjunctivitis. (Id. at 161, 173, 233.)

2. Framing the Issue

As discussed more fully supra in section II.C.2, the issue before the Court is what a POSITA would have done in 1998 to improve topical ophthalmic treatments. (See Pls.' Post-Trial Br. at 1-3.) This was particularly challenging given the unstable nature of azithromycin in water and the innumerable options of delivery systems. (See supra section II.D.1.)

3. Substantive Analysis

a. Sandoz's Arguments Regarding the Alleged Invalidity of the ISV Patents

i. The '113 and '443 Patents

(a) Motivation to Combine References

Sandoz argues that a POSITA would have been motivated to combine azithromycin and polycarbophil because POSITAs were, by 1996, aware of in-situ gelling systems, which would increase viscosity and a drug's residence time in the eye, thereby enhancing the efficacy of ophthalmic drugs. (See Sandoz's Post-Trial Br. at 34-35, 38-39.) Additionally, Sandoz asserts that POSITAs were specifically aware of DuraSite®, InSite's in-situ gelling system. (See id. at 35, 39.)

The '535 Patent is central to Sandoz's argument. (See id. at 34-36, 38-40 (providing claim-specific arguments).) Per Sandoz, the '535 Patent taught POSITAs to

use an in-situ gelling system comprising polycarbophil to topically deliver medicaments to the eye. (See id. at 35; DTX 82 at col. 12, line 42 to col. 13, line 29.) Sandoz argues that the '535 Patent teaches use of 0.1 to 6.5% crosslinking agent and a certain range of viscosity, and thus, according to Dr. Reed, the '535 Patent teaches POSITAs to "change the concentrations to get the viscosity that you wanted that still comes out as a drop." (Sandoz's Post-Trial Br. at 35-36 (quoting Trial Tr. at 1057).) It also teaches the use or incorporation of certain medicaments and antibiotics, including erythromycin, the parent of the macrolide class of antibiotics. (See id. at 35-36.)

(b) Reasonable Likelihood of Success

Sandoz argues that POSITAs would have reasonably expected the combination of azithromycin and DuraSite® to successfully deliver azithromycin to the eye's surface tissues. (Id. at 36-37.) Sandoz relies heavily on Dr. Reed's testimony to the effect that POSITAs were aware of the effectiveness of polycarbophil in DuraSite®, and "azithromycin was known to go into tissues"; thus, "this is taking an antibiotic and putting it in a known vehicle." (Id. at 37 (quoting Trial Tr. at 857, 910-11).) Sandoz also argues that certain references taught that use of polycarbophil facilitated reduced dosing frequency and allowed the once-daily topical dosing of azithromycin. (See id.)

ii. The '893 Patent

(a) Motivation to Combine References

Sandoz argues that the teachings in the '893 Patent regarding pH and MIC_{50} levels for 12 hours after administration are obvious because the '535 Patent taught both: (1) the

use of a pH between 3 and 6.5; and (2) the sustained release of medicaments in the eye, including antibiotics such as erythromycin. (See id. at 40-41.) Sandoz also asserts that: (1) pH levels between 5 and 7 were well known in the art; and (2) prior art references such as O'Day (the study of oral azithromycin in rabbits, DTX 183) taught that the desired MIC_{50} levels were a known property of azithromycin. (See id.)

(b) Reasonable Expectation of Success

Sandoz argues that certain pH ranges for ophthalmic medicaments are typical and that POSITAs routinely test formulations for pH and stability; thus POSITAs would have expected certain pH-specific formulations to function properly. (See id. at 41, 43-44.) Sandoz also asserts that POSITAs would reasonably have expected the combination of azithromycin and polycarbophil to yield sufficiently high concentrations of azithromycin in the eye's surface tissue to achieve the desired MIC_{50}. (See id. at 41-44.) Sandoz argues that it was obvious to treat infected ocular tissues topically with antibiotics, and that the '535 Patent taught the use of such antibiotics in a formulation including polycarbophil. (See id. at 44.) Finally, Sandoz asserts that the once-daily administration of topical azithromycin in polycarbophil is: (1) similar to the topical dosing of erythromycin; and (2) "not surprising, given that a person of ordinary skill in the art in 1996, would know that topical applications results in higher concentrations." (See id.)

iii. Secondary Considerations

Sandoz argues that Plaintiffs failed to introduce proof of secondary considerations of nonobviousness with respect to all of the claims asserted from the ISV Patents. (See id. at 42.)

b. Plaintiffs' Arguments in Favor of the Validity of the ISV Patents

i. Plaintiffs' Argument that Sandoz Improperly Analyzed the ISV Patents Using Hindsight

Plaintiffs argue that a POSITA, when developing new topical ophthalmic antibiotic formulations, would consider many different antibiotics and delivery systems. (See Pls.' Post-Trial Br. at 32-34.) Dr. Reed, however, admittedly "focused" on azithromycin, DuraSite®, and polycarbophil. Thus, Plaintiffs assert that Dr. Reed improperly analyzed the obviousness of the ISV Patents through the lens of hindsight because he failed to consider all of the options for both antibiotics and delivery systems that a POSITA would have considered. (See id. at 32-34 & n.21 (citing Ely Lily Co. v. Teva Pharms. USA, Inc., 619 F.3d 1329, 1340 (Fed.Cir. 2010); Life Techs., Inc. v. Clontech Labs., Inc., 224 F.3d 1320, 1325 (Fed.Cir. 2000)).)

ii. Prior Art Taught Away from Combining Azithromycin and Polycarbophil

Plaintiffs argue that developing topical ophthalmic formulations is an "incredibly difficult task." (Id. at 29 (quoting DTX 84 at xv).) Such development, in the period encompassing 1996-2001, required a POSITA to consider many factors, including: tonicity, viscosity, solvent type, buffer type, pH, preservatives, toxicity, irritation,

solubility of the active ingredient, and stability of the active ingredient. (See id. at 29-30.) Plaintiffs argue that an evaluation of these considerations would have led a POSITA away from combining azithromycin and polycarbophil. (See id. at 29-41.)

(a) Azithromycin Was Known to Be Insoluble in Water

Plaintiffs' primary argument rests on prior art showing that azithromycin is insoluble in water. (See id. at 31-32, 35, 36, 38-39.) This builds on the argument that Plaintiffs presented regarding the validity of the '411 Patent.

(b) A POSITA Would Have Considered and Selected Other Delivery Systems

Plaintiffs argue that a POSITA would not have been motivated to select polycarbophil from the "many" or "hundreds" of vehicle options that were available. They rely on the testimony of their formulation expert, Dr. Lee, who explained that a POSITA, if ignoring issues relating to azithromycin's insolubility/degradation in water, would have considered both colloidal systems and combination systems to be superior to the numerous types of gel systems, including polycarbophil. (See id. at 33-34.) Plaintiffs argue that Dr. Reed (1) focused on polycarbophil to the exclusion of other delivery systems, and (2) failed to explain why a POSITA would choose polycarbophil over the other, available options. (See id. at 34.)

(c) Neither the AquaSite® Label (DTX 50) Nor the Bowman Reference (DTX 189) Provided Motivation to Combine Azithromycin and Polycarbophil

Plaintiffs argue that neither the AquaSite® label nor the Bowman reference provided POSITAs with motivation to combine azithromycin and polycarbophil. (See id. at 34-36.) Plaintiffs assert that neither reference disclosed basic information necessary to evaluate the use of polycarbophil in a new formulation. Such information would include the efficacy, stability, and safety of polycarbophil when paired with an active ingredient. (See id. at 35-36.) Additionally, neither reference taught a POSITA to use a specific amount (by weight percentage or otherwise) of polycarbophil. (See id. at 34-35.)

(d) The '535 Patent Does Not Provide Motivation to Combine Azithromycin and Polycarbophil

Plaintiffs acknowledge that the '535 Patent generally teaches use of polycarbophil and other acrylic acid polymer systems in topical ophthalmic formulations. (See id. at 36.) However, they argue -- by reference to Dr. Lee's testimony and Dr. Reed's testimony -- that the '535 Patent did not teach a POSITA how to create the claimed inventions. (See id. at 36-38.) The '535 Patent taught broad ranges of both viscosity and concentration of crosslinking polymers. (See id. at 37.) Plaintiffs argue that, as a result, a POSITA would still need to determine where in those ranges the formulation should fall, and there were many possible combinations. (See id.)

Plaintiffs also contend that the '535 Patent would not have provided motivation to combine polycarbophil with azithromycin. (See id. at 37-38.) This argument rests on

two bases. First, Dr. Lee testified that a POSITA would focus on the examples of the '535 Patent, which only disclose use of the active ingredients fluorometholone and pilocarpine. Dr. Lee stated that those compounds are very different from azithromycin, and the use of such compounds would not lead a POSITA to conclude that one could also use azithromycin. (See id. at 37.) Second, Plaintiffs argue that the "laundry list" of medicaments claimed in the '535 Patent would not lead a POSITA to combine polycarbophil with azithromycin. When the '535 Patent issued, azithromycin was known to have antibiotic properties, yet it was not included in that list. (See id. at 37-38.)

(e) The '411 Patent Does Not Provide Motivation to Combine Azithromycin and Polycarbophil

Plaintiffs maintain that Dr. Reed's statements regarding his prior art cut-off date preclude Sandoz from relying on the '411 Patent as prior art against the ISV Patents. (See supra section II.D.1.a.)

Plaintiffs nevertheless argue that references in the '411 Patent to "Carbopol 934P" do not teach use of polycarbophil. (See Pls.' Post-Trial Br. at 39.) In 1988, it was known that "Carbopol 976" was polycarbophil. (See id. at 39.) However, it is undisputed that Carbopol 976 was renamed "Noveon AA-1" in 1992, long before the application that issued as the '411 Patent was filed. (See id. at 39; see also DTX 1 at [22], [60].) Carbopol 934P is not polycarbophil but is a different polymer altogether. (Pls.' Post-Trial Br. at 39-40.) Thus, references in the '411 Patent to "Carbopol" do not encompass polycarbophil and do not provide guidance relating to polycarbophil. (See Pls.' Post-Trial Br. at 39.)

iii. Reasonable Expectation of Success and Secondary Considerations of Nonobviousness

Dr. Lee testified that the resultant properties of AzaSite® are remarkable and unpredictable, especially when considering the properties of azithromycin and polycarbophil individually. (See id. at 42, 46-49.) Thus, there was no reasonable expectation of success for a formulation combining azithromycin and polycarbophil, and the results of such combination were unexpected.

Plaintiffs also argue that AzaSite® met a long-felt need for once-daily dosing of topical ophthalmic formulations. (See id. at 49-50.) They argue that, while Dr. Goren disagreed that there was such a long-felt need, Dr. Goren's testimony was rebutted by every other witness at trial, including Dr. Reed. (See id. at 50.)

c. Sandoz Engaged in Improper Hindsight Analysis of the ISV Patents

The Court concludes that Dr. Reed engaged in improper hindsight analysis in his consideration of the ISV Patents. Dr. Reed admitted on cross-examination that, in his review of the ISV Patents, he focused his research of the prior art on DuraSite® because he knew it contained polycarbophil. (Trial Tr. at 951-53.) Dr. Reed considered the Bowman article (DTX 189), the prior InSite '535 Patent (DTX 82), Dr. Ahmed's '411 Patent (DTX 1), and the report from the WHO Meeting (DTX 216). However, he admitted that none of the prior art disclosed a specific formulation using azithromycin and polycarbophil or DuraSite®.

Dr. Reed previously worked with InSite scientists, who had special knowledge about polycarbophil, and he relied heavily on their disclosures in formulating his opinions. However, viewing the art from the perspective of the patent's inventors is not the proper test.

See Life Techs., Inc. v. Clontech Labs., Inc., 224 F.3d 1320, 1325 (Fed.Cir. 2000) ("Because patentability is assessed from the perspective of the hypothetical person of ordinary skill in the art, information regarding the subjective motivations of inventors is not material.").

Sandoz relied heavily on the testimony of Dr. Reed in attempting to carry its burden of proving obviousness of the ISV Patents. The improper hindsight evaluation performed by Dr. Reed, and Sandoz's reliance on this testimony, is fatal to Sandoz's case, because Sandoz bears and has failed to carry the burden of proof. However, the Court has considered the totality of the record and need not rely on Sandoz's flawed hindsight analysis to reach the earlier-stated conclusion that the claimed inventions described in ISV Patents are not obvious.

d. Conclusions on Motivation to Combine References and Reasonable Expectation of Success

The Court finds that Sandoz failed to carry its burden of demonstrating the obviousness of the ISV Patents. At the time these patents were developed, a POSITA would not have been motivated to combine azithromycin and polycarbophil.

The prior art taught away from the use of azithromycin for topical ophthalmic treatments. Azithromycin was widely known to be unstable in water and insoluble. Thus, a POSITA would not have selected azithromycin for inclusion in an aqueous delivery vehicle.

The '411 Patent referenced "Carbopol 934P" in example 5, but the record demonstrates that this was not a reference to polycarbophil. As of the December 1997 filing of the '411 Patent, the name "Carbopol" no longer referred to polycarbophil following the name change of Carbopol 976 to Noveon® AA-1. (Trial Tr. at 1335-37.) Carbopol 934P is another polymer altogether.

While the '411 Patent lists examples of azithromycin in water-based vehicles (see DTX 1 at col. 3, lines 15-28 & col. 3, line 57 to col. 5, line 5), as previously discussed, the Court concludes that the '411 Patent is not prior art to the ISV Patents. However, even if the Court were to consider the '411 Patent and these examples, the result would not be altered. According to Dr. Ahmed, these examples are "prophetic." (See JTX 101 at 43.) Dr. Lee's testimony that a POSITA would have had concerns about the stability of azithromycin in those example formulations was uncontroverted. (Trial Tr. at 1331-33, 1338-40.) In fact, the '411 Patent's inventor, Dr. Ahmed, expressed concerns about the stability of azithromycin in these examples. (JTX 101 at 42-43, 52, 56.) The '411 Patent did not provide any stability data for these few examples. (Trial Tr. at 1063, 1331-33, 1339-40.) Thus, these examples fall short of satisfying Sandoz's burden under the clear-and-convincing standard.

Sandoz additionally failed to demonstrate that a POSITA would have been motivated to create a topical ophthalmic formulation using polycarbophil. Sandoz relied heavily on Dr. Reed's testimony on this issue. However, Dr. Reed's testimony has been largely discredited because his opinions were based on an improper hindsight analysis. (See supra section II.D.3.c; Trial Tr. at 951-53.) Moreover, while Dr. Reed claimed that it would have been obvious to a POSITA to create a topical ophthalmic formulation using azithromycin in an in-situ gelling system, when acting as a formulator developing and patenting in-situ gelling systems, he did not claim the combination of those systems with azithromycin even though it was an available antibiotic. (Trial Tr. at 1073-75.) Dr. Reed's own actions do not support his testimony of obviousness.

The Court credits Dr. Lee's testimony over that of Dr. Reed. Dr. Lee testified that, even if a formulator were to ignore azithromycin's instability in water, a formulator would prefer other delivery systems -- such as colloidal and combination systems -- over gelling systems -- like one using polycarbophil. (Id. at 1315-21.) Additionally, Dr. Lee explained that there were a multitude of examples of colloidal and combination systems, as well as approximately 40 options for gels that could be combined to create even more options. (Id.)

The Court also agrees with Plaintiffs that neither the AquaSite® label (DTX 50) nor the Bowman article (DTX 189) would have motivated a POSITA to select polycarbophil over other delivery systems. Neither the label nor the article contains information regarding polymer amounts or information regarding quantities of other ingredients. (Trial Tr. at 1047-53, 1312, 1321-22.) These references lack important stability data as well. Given the range of factors and options at play in these formulations, the absence of such information is fatal to any argument that the ISV Patents were obvious on the basis of these references.

Azithromycin is known to be unstable and insoluble, and DuraSite® -- which is contained in the AquaSite® product and described in the Bowman article -- is an aqueous-based system. (See id. at 1047-48, 1322-25.) However, there is nothing on the label or in the article that would explain how a formulation containing DuraSite® and azithromycin could function successfully given the instability of azithromycin. Both the label and the article lack stability, efficacy, and safety data regarding the combination of polycarbophil with any active ingredient. (Id. at 1051-54.) In fact, the AquaSite® product has no active ingredient, and there is no data demonstrating that its combination with any active ingredient, let alone

azithromycin, would be successful. (Id. at 1047-51, 1322-24.) And the Bowman article specifically states the success of a DuraSite delivery system is dependent on the physico-chemical properties of the chosen drug. (DTX 189 at 158.)

The Court further finds that the pH ranges in the '893 Patent would not have been obvious to a POSITA in 1998. The pH of a formulation most suitable for comfort is a pH of 7.4, yet azithromycin is most soluble at a pH of 5.0 or below. (Trial Tr. at 742-44, 1308-09.) While nothing in the art taught that azithromycin would be stable in a solution at a pH of 6.3, the '893 Patent claims that as the pH of the formulation. (DTX 4 at col. 28, lines 48-53.) Moreover, the '893 Patent's pH is higher than the '535 Patent's preferred embodiment pH range from 4.0 to 6.0. (DTX 82 at col. 7, lines 50-51.) Thus, Dr. Reed's testimony that he would adjust the pH level to reach the desired viscosity based on '535 Patent is unsupported with reference to the '535 Patent. (See Trial Tr. at 926-27.) Additionally, the pH of a formulation affects a variety of factors, including comfort, stability, polymer performance, and active ingredient solubility. (Id. at 744, 1307-08.) A researcher would not be able to anticipate a proper balance of these factors. (Id. at 1308-10.) Therefore, Sandoz has failed to demonstrate that the pH of the '893 Patent was obvious.

The Court also concludes that Sandoz failed to demonstrate that it would have been obvious to a POSITA that concentrations of azithromycin would remain above MIC_{50} for at least 12 hours after topical administration. Dr. Reed's testimony on this issue was based on a study of the oral administration of azithromycin on rabbits. However, the Court credits the testimony of Dr. Asbell -- that a POSITA would not simply assume that delivering high

concentrations of a drug to the eye, topically, would ensure that the drug would penetrate the ocular tissue -- over that of Dr. Reed. (See, e.g., id. at 643.) The record is replete with references to the barriers in the anatomy of the eye to ocular penetration. Moreover, Sandoz failed to show any correlation between concentrations of antibiotics following topical and oral administration.

For these reasons, the Court finds that Sandoz did not meet its burden of demonstrating, by clear and convincing evidence, that a POSITA would have been motivated to combine azithromycin and polycarbophil, or that a POSITA would have a reasonable expectation of success in such a formulation.

The Court further concludes that the secondary considerations of unexpected results and long-felt need favor Plaintiffs' position. While Sandoz argues that Plaintiffs have failed to establish secondary considerations, (see Sandoz's Post-Trial Br. at 42), Plaintiffs, as the patent holders, are "under no compulsion either to prove a new and surprising result or to prove the criticality" of the invention. Am. Hosp. Supply Corp. v. Travenol Labs., Inc., 745 F.2d 1, 8 (Fed.Cir. 1984). Rather, Sandoz, as the patent challenger, bears the burden of proving that the results were not in fact unexpected. Id. Sandoz has failed to meet this burden.

The inventions at issue had several unexpected properties as compared to the teachings about azithromycin in the prior art. Specifically, the concentrations of azithromycin were unexpectedly high when topically applied using polycarbophil. (Trial Tr. at 1172-76.) In fact, there was a 60-fold increase in azithromycin concentrations 24 hours after a topical dose

than after an oral dose. (Id. at 1172-73; PTX 125.) Dr. Abelson testified that "[t]here is absolutely no question that this is fully unexpected. . . . There's no other drug in my experience in 40 years of looking at drugs, or that of my colleagues, that has been like this." (Trial Tr. at 1176.) The Court finds that this 60-fold increase is indicative of unexpected results, further demonstrating the nonobviousness of the patents at issue. See Daiichi Sankyo Co. v. Mylan Pharm. Inc., 670 F.Supp.2d 359, 382-83 (D.N.J. 2009) (two to three fold improvement "unexpected"), aff'd, 619 F.3d 1346 (Fed.Cir. 2010); Proctor & Gamble Co. v. Teva Pharm. USA, Inc., 536 F.Supp.2d 476, 495-96 (D. Del. 2008) (three-times improvement "unexpected"), aff'd, 566 F.3d 989, 994, 997-98 (Fed.Cir. 2009).

In addition to the unexpectedly high concentrations, AzaSite® has increased activity against bacteria that were previously believed to be resistant to azithromycin. (Trial Tr. at 1188-89; PTX 118.) These results were surprising to experts because the manner in which azithromycin's antibiotic effect is improved when combined with polycarbophil remains unknown. (See Trial Tr. at 1189.) Dr. Lee also testified that the results here were remarkable, particularly because somehow, the formulation was able to overcome two of its main barriers, its stability and solubility in water. (Id. at 1350-51.)

The Court lastly concludes that the inventions at issue satisfied a long-felt need for a topical formulation of azithromycin that could be dosed once daily to treat ocular infections. Prior to these inventions, topical ophthalmic treatments required extended dosing multiple times per day for many days. (Id. at 664-69.) This led to issues of patient compliance, which resulted in bacterial resistance and incomplete treatment of the ocular infection. (Id. at 488,

669.)[17] Once-daily dosing of a topical ophthalmic treatment using azithromycin resolved these issues of frequent dosing and patient compliance. As a result of these considerations, the Court concludes that Sandoz has failed to show that the patents at issue are obvious. See In re Dow Chem. Co., 837 F.2d 469, 472 (Fed.Cir. 1988) ("Recognition of need, and difficulties encountered by those skilled in the field, are classical indicia of unobviousness.")

III. CONCLUSION

For the foregoing reasons, the Court has determined that the claims asserted from the patents-in-suit are valid and that Sandoz has failed to satisfy its burden of proving obviousness by clear and convincing evidence. The Court will issue an appropriate order and judgment.

s/ Mary L. Cooper
MARY L. COOPER
United States District Judge

Dated: October 4, 2013

[17] The Court does not credit the testimony of Dr. Goren that frequent dosing and patient compliance were not significant issues, as his testimony was contradicted by every other witness at trial, including the two other experts for Sandoz. (Trial Tr. at 488, 669-70, 768, 1299.)